Access DB# ____________

SEARCH REQUEST FORM

Scientific and Technical Information Center 60398

Requester's Full Name: BERCH Examiner #: 59193 Date: 12/14/02
Art Unit: 1624 Phone Number 30 84718 Serial Number: 722438
Mail Box and Bldg/Room Location: 4D15 4E12 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. MEB

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: ____________

Inventors (please provide full names): ____________

Earliest Priority Filing Date: ____________

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

MARY - I need the oldest hits for Bib 5 of 6 - not the youngest

There is at least one hit: J. Chromatography 572, 195-202 (1991)

I need a search on optically active form of zopiclone. ~~D, L, R or S in name~~ → It must have D or L in name OR S or R in name (not both)

MARY

PY = 1991 or earlier

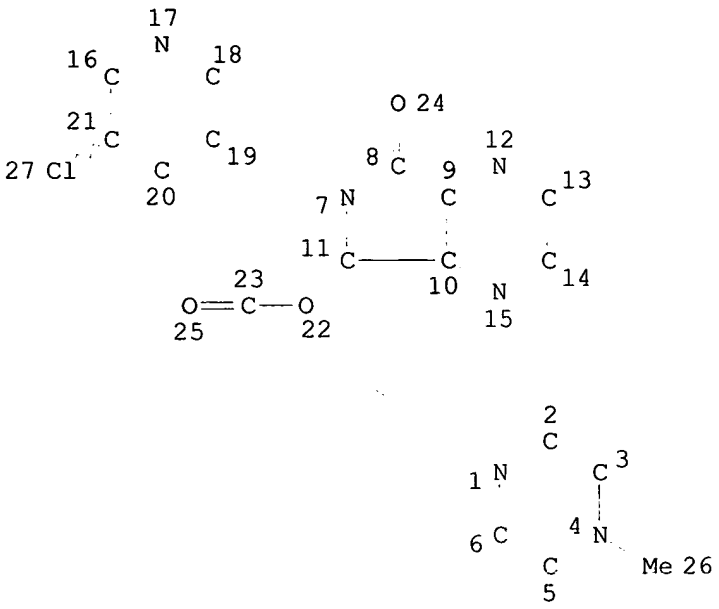
1239

****

STAFF USE ONLY		Type of Search		Vendors and cost where applicable	
Searcher:	Mary	NA Sequence (#)		STN	358.25
Searcher Phone #:		AA Sequence (#)		Dialog	
Searcher Location:		Structure (#)	2	Questel/Orbit	
Date Searcher Picked Up:		Bibliographic		Dr.Link	
Date Completed:	12/21	Litigation		Lexis/Nexis	
Searcher Prep & Review Time:		Fulltext		Sequence Systems	
Clerical Prep Time:		Patent Family		WWW/Internet	
Online Time:	54	Other		Other (specify)	

PTO-1590 (1-2000)

=> d 14 que stat;s l4(l)("d" or "l" or "s"or "r")/cn
L3 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

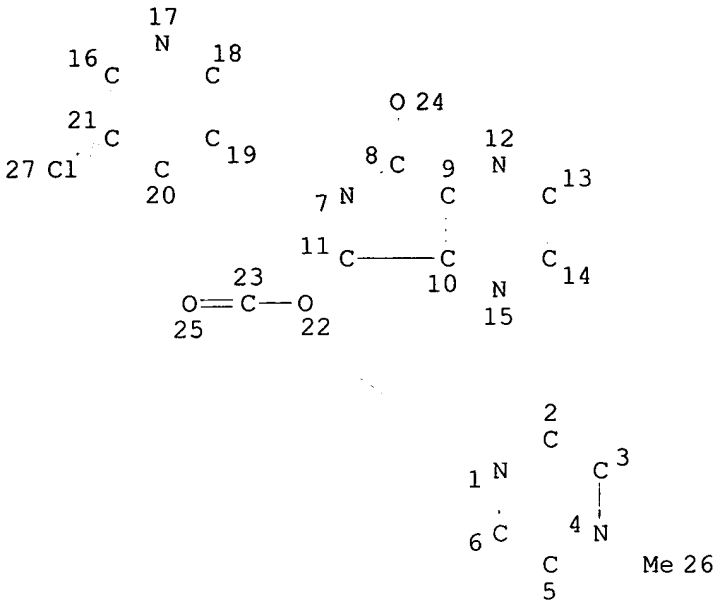
STEREO ATTRIBUTES: NONE
L4 12 SEA FILE=REGISTRY SSS FUL L3

100.0% PROCESSED 53 ITERATIONS 12 ANSWERS
SEARCH TIME: 00.00.03

PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L4(L)("D"'
0 "D"/CN
0 "L"/CN
0 "S"/CN
0 "R"/CN
L5 0 L4(L)("D" OR "L" OR "S"OR "R")/CN

=> d 14 que stat;s l4(l)("d" or "l" or "s"or "r")
L3 STR

Searched by: Mary Hale 308-4258 CM-1 12D16



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 27

STEREO ATTRIBUTES: NONE
L4 12 SEA FILE=REGISTRY SSS FUL L3

100.0% PROCESSED 53 ITERATIONS 12 ANSWERS
SEARCH TIME: 00.00.03

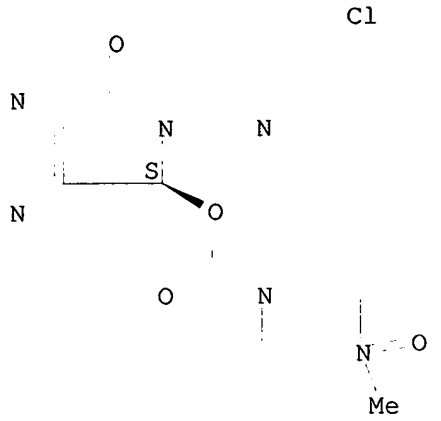
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L4(L)("D"'
1232051 "D"
1071249 "L"
1256832 "S"
408766 "R"
L6 6 L4(L)("D" OR "L" OR "S"OR "R")

=> d 1-6 ide cbib abs;fil biosis,caplus,medl,jicst,embase;s l6

L6 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 151851-70-6 REGISTRY
CN **1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester, 4-oxide, (S)- (9CI)**
(CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5H-Pyrrolo[3,4-b]pyrazine, 1-piperazinecarboxylic acid deriv.
FS STEREOSEARCH
MF C17 H17 Cl N6 O4
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Searched by: Mary Hale 308-4258 CM-1 12D16

Absolute stereochemistry.



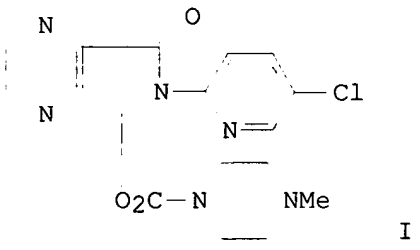
3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 124:193152 Enantioselective determination of zopiclone and its metabolites in urine by capillary electrophoresis. Hempel, G.; Blaschke, G. (Munster, D-48149, Germany). J. Chromatogr., B: Biomed. Appl., 675(1), 139-46 (English) 1996. CODEN: JCBBEP. ISSN: 0378-4347.

AB A method has been developed for the stereoselective detn. of zopiclone and its main metabolites in urine. After the addn. of the internal std. zolpidem the urine samples were extd. at pH 8 with chloroform-isopropanol (9:1). Analyses were carried out using capillary electrophoresis (CE) with .beta.-cyclodextrin as the chiral selector. The analytes were detected using UV laser-induced fluorescence detection with a He-Cd laser operated at 325 nm. Urine samples of two volunteers after oral administration of 7.5 mg zopiclone were investigated. The S-(+)-enantiomers of zopiclone and its metabolites were always excreted in higher amts. than the R-(-)-enantiomers. With the same method the zopiclone enantiomers were quantified in saliva. Compared to high-performance liq. chromatog., the CE method is very fast and simple.

REFERENCE 2: 120:235291 Pharmacokinetics of zopiclone and its enantiomers in Caucasian young healthy volunteers. Fernandez, C.; Maradeix, V.; Gemenez, F.; Thuillier, A.; Farinotti, R. (Serv. Pharm. Pharmacocinet., Hop. Pitie Salpetriere, Paris, 75651, Fr.). Drug Metab. Dispos., 21(6), 1125-8 (English) 1993. CODEN: DMDSAI. ISSN: 0090-9556.

GI



I

Searched by: Mary Hale 308-4258 CM-1 12D16

AB The disposition of the enantiomers of zopiclone (I) and its two chiral metabolites was investigated after oral administration of a single dose of 15 mg of a racemic mixt. (twice the usual therapeutic regimen) in 12 adult Caucasian volunteers. Detn. of concns. of zopiclone enantiomers in plasma showed that zopiclone pharmacokinetics is stereoselective with AUC0-.infin. values of 691.3 and 209.5 ng.mL-1.h ($p < 0.001$), Cmax value of 87.3 and 44.0 ng.mL-1 ($p < 0.001$), oral CLtot/F values of 195.5 and 659.8 mL.min-1 ($p < 0.001$), Vd/F values of 98.6 and 192.8 L ($p < 0.01$) and elimination half-life of 399.2 and 225.6 min ($p < 0.01$) for (+)-zopiclone and (-)-zopiclone, resp. On the contrary, absorption half-life and Tmax values were not significantly different. In 48-h urine, 3.6% of unchanged zopiclone was excreted, whereas 14.2% and 13.8% of both metabolites, N-desmethylzopiclone and N-oxideopiclone, resp., were found. Quantities of (+)-zopiclone excreted in urine were always higher compared with its antipode (-)-zopiclone for the 12 volunteers ($p < 0.001$). For the metabolites, quantities of both enantiomers were either equal or different and when different, it was always in favor of the (+)-enantiomer.

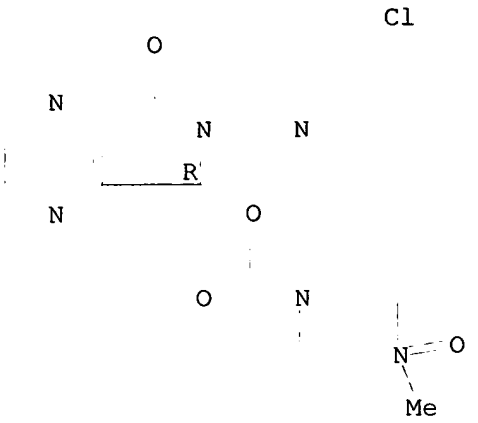
REFERENCE 3: 120:22978 Determination of the enantiomers of zopiclone and its two chiral metabolites in urine using an automated coupled achiral-chiral chromatographic system. Fernandez, Christine; Gimenez, Francois; Baune, Bruno; Maradeix, Valerie; Thuillier, Alain (Serv. Pharm., Hop. Pitie Salpetriere, Paris, 75013, Fr.). J. Chromatogr., Biomed. Appl., 617(2), 271-8 (English) 1993. CODEN: JCBADL. ISSN: 0378-4347.

AB The enantiomers of zopiclone and its two chiral N-desmethyl and N-oxide metabolites were detd. in urine using a coupled achiral-chiral liq. chromatog. method. After liq.-liq. extn., zopiclone and its two metabolites were quantified on a cyanopropyl column. After fluorimetric detection on the achiral system, the eluent was switched through a silica precolumn in order to trap and conc. the analytes. Each fraction was then backflushed sep. onto a carbamate cellulose chiral stationary phase in order to det. the enantiomeric ratios. The coupled system was automated with an autosampler and a switching value programmed by an integrator. The method was validated, and a first trial was performed on urine samples of a volunteer treated with 15 mg of racemic zopiclone.

L6 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 151851-69-3 REGISTRY
CN **1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester, 4-oxide, (R)- (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 5H-Pyrrolo[3,4-b]pyrazine, 1-piperazinecarboxylic acid deriv.
FS STEREOSEARCH
MF C17 H17 Cl N6 O4
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16



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AB A method has been developed for the stereoselective detn. of zopiclone and its main metabolites in urine. After the addn. of the internal std. zolpidem the urine samples were extd. at pH 8 with chloroform-isopropanol (9:1). Analyses were carried out using capillary electrophoresis (CE) with .beta.-cyclodextrin as the chiral selector. The analytes were detected using UV laser-induced fluorescence detection with a He-Cd laser operated at 325 nm. Urine samples of two volunteers after oral administration of 7.5 mg zopiclone were investigated. The S-(+)-enantiomers of zopiclone and its metabolites were always excreted in higher amts. than the R-(-)-enantiomers. With the same method the zopiclone enantiomers were quantified in saliva. Compared to high-performance liq. chromatog., the CE method is very fast and simple.

REFERENCE 2: 120:235291 Pharmacokinetics of zopiclone and its enantiomers in Caucasian young healthy volunteers. Fernandez, C.; Maradeix, V.; Gemenez, F.; Thuillier, A.; Farinotti, R. (Serv. Pharm. Pharmacocinet., Hop. Pitie Salpetriere, Paris, 75651, Fr.). Drug Metab. Dispos., 21(6), 1125-8 (English) 1993. CODEN: DMDSAI. ISSN: 0090-9556.

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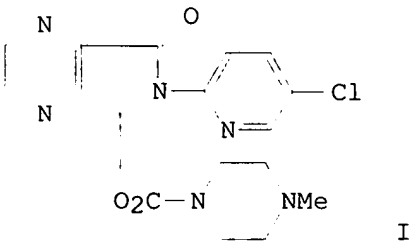

I

AB The disposition of the enantiomers of zopiclone (I) and its two chiral metabolites was investigated after oral administration of a single dose of

Searched by: Mary Hale 308-4258 CM-1 12D16

15 mg of a racemic mixt. (twice the usual therapeutic regimen) in 12 adult Caucasian volunteers. Detn. of concns. of zopiclone enantiomers in plasma showed that zopiclone pharmacokinetics is stereoselective with AUC0-.infin. values of 691.3 and 209.5 ng.mL-1.h ($p < 0.001$), Cmax value of 87.3 and 44.0 ng.mL-1 ($p < 0.001$), oral CLtot/F values of 195.5 and 659.8 mL.min-1 ($p < 0.001$), Vd/F values of 98.6 and 192.8 L ($p < 0.01$) and elimination half-life of 399.2 and 225.6 min ($p < 0.01$) for (+)-zopiclone and (-)-zopiclone, resp. On the contrary, absorption half-life and Tmax values were not significantly different. In 48-h urine, 3.6% of unchanged zopiclone was excreted, whereas 14.2% and 13.8% of both metabolites, N-desmethylzopiclone and N-oxideopiclone, resp., were found. Quantities of (+)-zopiclone excreted in urine were always higher compared with its antipode (-)-zopiclone for the 12 volunteers ($p < 0.001$). For the metabolites, quantities of both enantiomers were either equal or different and when different, it was always in favor of the (+)-enantiomer.

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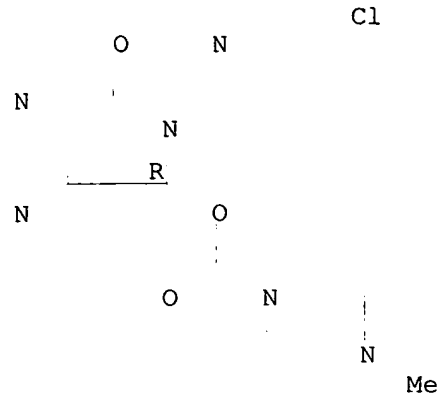
L6 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 144025-94-5 REGISTRY
CN **Butanedioic acid, 2,3-bis(benzoyloxy)-, [S-(R*,R*)]-, compd. with (-)-6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methyl-1-piperazinecarboxylate (1:1) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester, (-)-, [S-(R*,R*)]-2,3-bis(benzoyloxy)butanedioate (1:1) (9CI)**
CN 5H-Pyrrolo[3,4-b]pyrazine, 1-piperazinecarboxylic acid deriv.
FS STEREOSEARCH
MF C18 H14 O8 . C17 H17 Cl N6 O3
SR CA
LC STN Files: CA, CAPLUS, DRUGPAT, DRUGUPDATES, USPATFULL

CM 1

CRN 138680-08-7
CMF C17 H17 Cl N6 O3

Absolute stereochemistry.

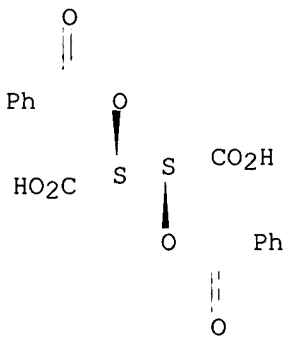
Searched by: Mary Hale 308-4258 CM-1 12D16



CM 2

CRN 17026-42-5
CMF C18 H14 O8

Absolute stereochemistry. Rotation (+).



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 117:191870 Preparation of (-)-zopiclone. Cotrel, Claude; Roussel, Gerard (Rhone-Poulenc Rorer S. A., Fr.). Eur. Pat. Appl. EP 495717 A1 19920722, 5 pp. DESIGNATED STATES: R: PT. (French). CODEN: EPXXDW. APPLICATION: EP 1992-400111 19920116. PRIORITY: FR 1991-490 19910117.

AB The title compd., prepd. by optical resoln. of racemic zopiclone as the D-(+)-O,O'-dibenzolyltartrate salt, is about twice as active as the racemate and had LD50 of .apprx.1.5 g/kg orally in mice.

L6 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 144025-93-4 REGISTRY
CN **Butanedioic acid, 2,3-bis(benzoyloxy)-, [S-(R*,R*)]-, compd. with (+)-6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl 4-methyl-1-piperazinecarboxylate (1:1) (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester, (+)-, [S-(R*,R*)]-2,3-bis(benzoyloxy)butanedioate (1:1) (9CI)**
CN 5H-Pyrrolo[3,4-b]pyrazine, 1-piperazinecarboxylic acid deriv.
FS STEREOSEARCH

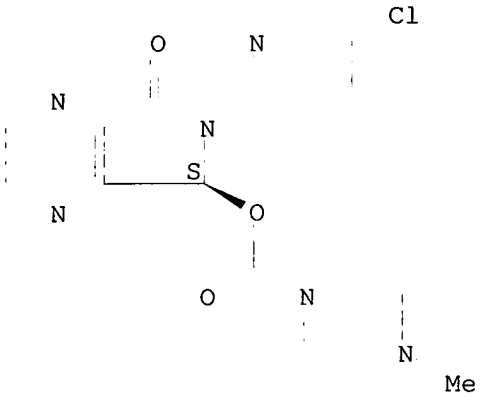
Searched by: Mary Hale 308-4258 CM-1 12D16

MF C18 H14 O8 . C17 H17 Cl N6 O3
SR CA
LC STN Files: CA, CAPLUS, DRUGPAT, DRUGUPDATES, USPATFULL

CM 1

CRN 138729-47-2
CMF C17 H17 Cl N6 O3

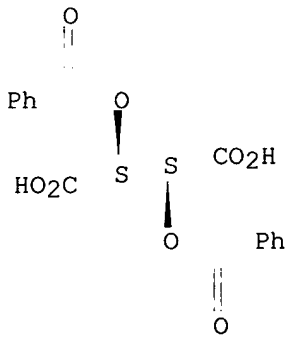
Absolute stereochemistry. Rotation (+).



CM 2

CRN 17026-42-5
CMF C18 H14 O8

Absolute stereochemistry. Rotation (+).



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 117:191870 Preparation of (-)-zopiclone. Cotrel, Claude; Roussel, Gerard (Rhone-Poulenc Rorer S. A., Fr.). Eur. Pat. Appl. EP 495717 A1 19920722, 5 pp. DESIGNATED STATES: R: PT. (French). CODEN: EPXXDW. APPLICATION: EP 1992-400111 19920116. PRIORITY: FR 1991-490 19910117.

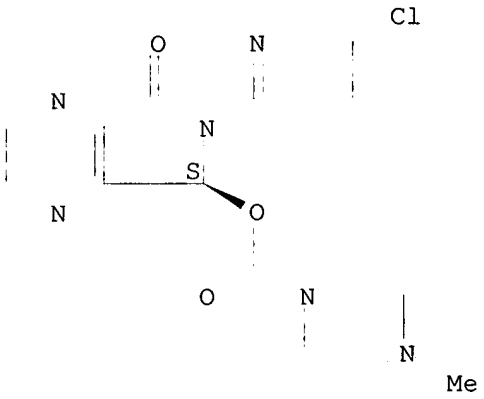
AB The title compd., prepd. by optical resoln. of racemic zopiclone as the D-(+)-O,O'-dibenzolyltartrate salt, is about twice as active as the racemate and had LD50 of .apprx.1.5 g/kg orally in mice.

L6 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2002 ACS

Searched by: Mary Hale 308-4258 CM-1 12D16

RN 138729-47-2 REGISTRY
CN 1-Piperazinecarboxylic acid, 4-methyl-, (5S)-6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester, (S)-**
CN 5H-Pyrrolo[3,4-b]pyrazine, 1-piperazinecarboxylic acid deriv.
OTHER NAMES:
CN (+)-Zopiclone
FS STEREOSEARCH
MF C17 H17 Cl N6 O3
CI COM
SR CA
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CEN, CIN, DRUGNL, DRUGPAT, DRUGUPDATES, PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

25 REFERENCES IN FILE CA (1967 TO DATE)
25 REFERENCES IN FILE CAPLUS (1967 TO DATE)

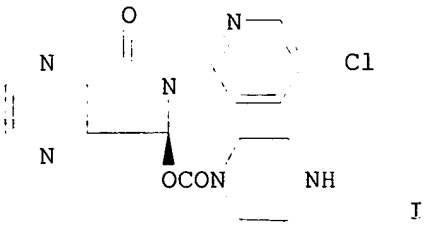
REFERENCE 1: 135:55957 Sedative and anxiolytic effects of zopiclone's enantiomers and metabolite. Carlson, J. N.; Haskew, R.; Wacker, J.; Maisonneuve, I. M.; Glick, S. D.; Jerussi, T. P. (Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, NY, 12208, USA). Eur. J. Pharmacol., 415(2,3), 181-189 (English) 2001. CODEN: EJPHAZ. ISSN: 0014-2999. Publisher: Elsevier Science B.V..
AB We evaluated racemic zopiclone, its (S)- and (R)-enantiomers and a metabolite, (S)-desmethylzopiclone, for their actions on locomotor activity, rotarod performance, the elevated plus maze and the Vogel conflict test of anxiety, and electroconvulsive shock-induced seizures duration. Zopiclone and its (R)- and (S)-enantiomers reduced locomotor activity, and zopiclone and its (S)-enantiomer disrupted rotarod performance at 10 mg/kg. (S)-desmethylzopiclone did not alter these measures at doses of less than 200 mg/kg. (S)-desmethylzopiclone altered plus maze performance at the lowest dose of all the zopiclone derivs. tested, caused a dose-related effect on the Vogel conflict test and caused a dose-related redn. of electroconvulsive shock-induced seizure durations. The data indicate that (S)-desmethylzopiclone can bring about an

Searched by: Mary Hale 308-4258 CM-1 12D16

anxiolytic effect without a substantial degree of central nervous system depression, and suggest that the agent may be particularly useful clin. in the treatment of anxiety.

REFERENCE 2: 134:311174 Synthesis of enantiomerically pure desmethylzopiclone and determination of its absolute configuration. Hong, Y.; Bakale, R. P.; Fang, Q. K.; Xiang, T.; Han, Z.; McConville, F. X.; Senanayake, C. H.; Wald, S. A. (Chemical Process Research and Development, Sepracor Inc., Marlborough, MA, 01752, USA). Tetrahedron: Asymmetry, 11(23), 4623-4627 (English) 2000. CODEN: TASYE3. ISSN: 0957-4166. Publisher: Elsevier Science Ltd..

GI



I

AB Two synthetic methods have been established for the prepn. of enantiomerically pure desmethylzopiclone, a metabolite of zopiclone. In Method A, (S)-desmethylzopiclone (I) was prepd. by demethylation of (S)-zopiclone with 1-chloroethyl chloroformate in high yield. Enantiomerically pure zopiclone (>99% ee) was obtained through a highly efficient resoln. process in >36% overall yield. In Method B, racemic desmethylzopiclone was resolved with L-N-benzyloxycarbonyl phenylalanine, followed by recrystn. in good yield. The abs. stereochem. of the (+)-enantiomer was first detd. to be the (S)-configuration by X-ray crystallog.

REFERENCE 3: 134:9361 Methods of making and using N-desmethylzopiclone. Jerussi, Thomas P.; Senanayake, Chrisantha H.; Rubin, Paul D.; Hong, Yaping; Bakale, Roger A.; Xiang, Tingjian; McConville, Fran A. (Sepracor Inc., USA). PCT Int. Appl. WO 2000069442 A1 20001123, 44 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US12820 20000511. PRIORITY: US 1999-PV134239 19990514; US 1999-PV135037 19990520; US 2000-548607 20000413.

AB The invention is directed to compns. comprising, and methods of using, racemic N-desmethylzopiclone, optically pure (+)-N-desmethylzopiclone, and optically pure (-)-N-desmethylzopiclone in the treatment and prevention of diseases and conditions in mammals. The invention is further directed to novel methods of prepg. N-desmethylzopiclone, optically pure (+)-N-desmethylzopiclone, and optically pure (-)-N-desmethylzopiclone. The compds. are administered to patients suffering from, anxiety, convulsions, depression, behavioral disorders, sleep disorders, etc.

REFERENCE 4: 133:183136 Separation of enantiomers of drugs by capillary electrophoresis with permethyl-gamma-cyclodextrin as chiral solvating agent. Koppenhoefer, Bernhard; Jakob, Andreas; Zhu, Xiaofeng; Lin,

Bingcheng (Institute of Organic Chemistry, University of Tubingen, Germany). Journal of High Resolution Chromatography, 23(6), 413-429 (English) 2000. CODEN: JHRCE7. ISSN: 0935-6304. Publisher: Wiley-VCH Verlag GmbH.

AB High-throughput screening is a promising new approach in anal. chem. Within the framework of an extended screening program (The German-Chinese Drug Screening Program), the enantiosepn. of 86 drugs was investigated by capillary zone electrophoresis in the presence of the chiral solvating agent (CSA) octakis-(2,3,6-tri-O-methyl)-.gamma.-cyclodextrin (TM-.gamma.-CD). By this means, 15 drugs could be sepd. into enantiomeric pairs. Approx. measures for the degree of interaction (migration retardation factor, Rm) and for the degree of enantiomer recognition (migration sepn. factors, .alpha.m) revealed intriguing patterns that were compared with those found for native .gamma.-cyclodextrin (.gamma.-CD). Although there is a distinct influence of the analyte structure on the electrophoretic data, interpretation remains difficult. Most remarkably, permethylation of .gamma.-CD leads neither to a higher affinity nor to better chiral recognition, in contrast to the findings with .alpha.-CD.

REFERENCE 5: 132:6266 Racemic switches. Historical perspectives and current status. Cannarsa, Michael J. (PPG-Sipsy Chemical Co., West Chester, PA, 19382, USA). Chim. Oggi, 17(9), 28-32 (English) 1999. CODEN: CHOGDS. ISSN: 0392-839X. Publisher: TeknoScienze.

AB A review with 6 refs., describing historical development of asym. synthesis technol. and recent developments in racemic switches of perprazole, fluoxetine, D-methylphenidate, levalbuterol, levobupivacaine, citalopram, cetirizine, norcisapride-(+), zopiclone, and formoterol-(R,R). The single enantiomers (S)-ibuprofen, dexketoprofen, dexfenfluramine, and verapamil continue to struggle for a place in the market.

REFERENCE 6: 131:277050 Separation of drugs by capillary electrophoresis. Part 10. Permethyl-alpha-cyclodextrin as chiral solvating agent. Zhu, Xiao Feng; Lin, Bing Cheng; Jakob, Andreas; Wuerthner, Stefan; Koppenhoefer, Bernhard (Dalian Inst. Chemical Phys., Dalian, Peop. Rep. China). Electrophoresis, 20(9), 1878-1889 (English) 1999. CODEN: ELCTDN. ISSN: 0173-0835. Publisher: Wiley-VCH Verlag GmbH.

AB Following the German-Chinese Drug Screening Program, 86 racemic drugs were investigated in capillary zone electrophoresis in the presence of the chiral solvating agent (CSA) hexakis-(2,3,6-tri-O-methyl)-.alpha.-cyclodextrin (TM-.alpha.-CD). Of the 86 drugs, 23 were sepd. into enantiomeric pairs. A comparison of the migration sepn. factors (.alpha.m) and the migration retardation factors (Rm) with previously published data for native .alpha.-CD revealed that the "upper-rim" hydroxyl groups do not necessarily facilitate the recognition of the drug enantiomers by the chiral host. In contrast, an overall increase in affinity for the permethylated host led to a higher rate of successful enantiomer sepns. A key substructure (4H) was identified in the analyte structure domain, with a crucial influence on the behavior of a particular drug.

REFERENCE 7: 130:261430 Stereoselective binding of zopiclone to human plasma proteins. Fernandez, Christine; Gimenez, Francois; Thuillier, Alain; Farinotti, Robert (Hopital Pitie-Salpetriere, Service Pharmacie-Pharmacocinetique, Paris, 75013, Fr.). Chirality, 11(2), 129-132 (English) 1999. CODEN: CHRLEP. ISSN: 0899-0042. Publisher: Wiley-Liss, Inc..

AB The binding of racemic zopiclone (ZOP) and of its two enantiomers to plasma proteins, albumin and .alpha.1-acid glycoprotein were compared. Our work shows that the binding of ZOP to human plasma proteins is stereoselective. The total plasma protein binding percentages were 79.3.+-.5.5%, 83.8.+-.5.2%, and 75.1.+-.2.1%, for racemic zopiclone, (-)-zopiclone and (+)-zopiclone, resp. These results were confirmed by

the anal. of samples obtained from healthy volunteers after the oral administration of ZOP. The anticoagulant used for sampling was also shown to have an influence on the percentage binding and on its stereoselectivity. Considering albumin and .alpha.1-acid glycoprotein sep., stereoselectivity was also obsd.

REFERENCE 8: 129:221244 Separation of enantiomers of drugs by capillary electrophoresis, part 7: gamma-cyclodextrin as chiral solvating agent. Koppenhoefer, Bernhard; Epperlein, Ulrich; Jakob, Andreas; Wuerthner, Stefan; Xiaofeng, Zhu; Bingcheng, Lin (Institute for Organic Chemistry, University of Tiibingen, Tuibingen, Germany). Chirality, 10(6), 548-554 (English) 1998. CODEN: CHRLEP. ISSN: 0899-0042. Publisher: Wiley-Liss, Inc..

AB Following an extended chiral drug screening program by capillary zone electrophoresis (CZE), the enantiosepn. of 86 racemic drugs was tested with .gamma.-cyclodextrin as a chiral solvating agent. Unified conditions were applied to all expts. In total, 18 drug racemates were sepd., 13 entries thereof that had not been sepd. at the lower CSA concn. applied in an earlier stage of the project. A comparison of the data with the results obtained for .alpha.- and .beta.-cyclodextrin points to the significance of partial penetration ("side-on binding") of aryl groups into the cyclodextrin cavity.

REFERENCE 9: 129:140784 Separation of enantiomers of drugs by capillary electrophoresis. Part 8. .beta.-Cyclodextrin as chiral solvating agent. Lin, B.; Zhu, X.; Wuerthner, S.; Epperlein, U.; Koppenhoefer, B. (Institute of Chemical Physics, Dalian, Peop. Rep. China). Talanta, 46(4), 743-749 (English) 1998. CODEN: TLNTA2. ISSN: 0039-9140. Publisher: Elsevier Science B.V..

AB As part of a comprehensive screening program on the sepn. of chiral drugs by capillary zone electrophoresis the enantiomeric sepn. of 54 drug racemates using .beta.-cyclodextrin as a chiral solvating agent was investigated. This study complements previous studies on 34 drug racemates. Fourteen out of the 54 analytes investigated were sepd. into the enantiomers, yielding on overall success rate of 24.4% for a total of 86 drug racemates investigated.

REFERENCE 10: 128:167442 (+)-6-(5-Chloropyrid-2-yl)-7-oxo-5-[[(vinyloxy)carbonyl]oxy]-5,6-dihydropyrrolo[3,4-b]pyrazine and its use in a process for preparation of (+)-6-(5-chloropyrid-2-yl)-5-[[(4-methylpiperazin-1-yl)carbonyl]oxy]-7-oxo-5,6-dihydropyrrolo[3,4-b]pyrazine [(+)-zopiclone]. Gotor Santamaria, Vicente; Brieva Collado, Rosario; Linares Lopez, Francisco J.; Garcia Campos, Roberto; Bayod Jasanada, Miguel Santos (Astupaharma, S.A., Spain). Span. ES 2101653 A1 19970701, 6 pp. (Spanish). CODEN: SPXXAD. APPLICATION: ES 1995-1385 19950710.

GI

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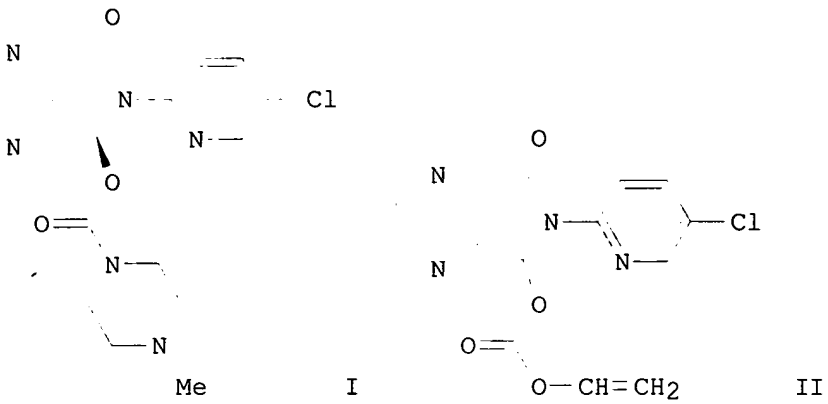

Me I O—CH=CH2 II

AB The hypnotic drug (+)-zopiclone, i.e. (+)-I, is prepd. in 3 steps, under mild conditions and with good yields, via the title intermediate (+)-II. Thus, 6-(5-chloropyrid-2-yl)-5-hydroxy-7-oxo-5,6-dihydropyrrolo[3,4-b]pyrazine was esterified with vinyl chloroformate in pyridine to give II, which was subjected to enzymic resoln. using lipase of Candida antarctica to leave (+)-II with >95% enantiomeric excess (ee). Condensation of the latter with N-methylpiperazine gave (+)-I, also with >95% ee.

L6 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2002 ACS
RN 138680-08-7 REGISTRY
CN 1-Piperazinecarboxylic acid, 4-methyl-, (5R)-6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN **1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester, (R)-**
CN 5H-Pyrrolo[3,4-b]pyrazine, 1-piperazinecarboxylic acid deriv.
OTHER NAMES:
CN (-)-Zopiclone
CN **(R)-Zopiclone**
FS STEREOSEARCH
MF C17 H17 Cl N6 O3
CI COM
SR CA
LC STN Files: ADISNEWS, BEILSTEIN*, BIOSIS, CA, CAPLUS, DRUGPAT, DRUGUPDATES, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.

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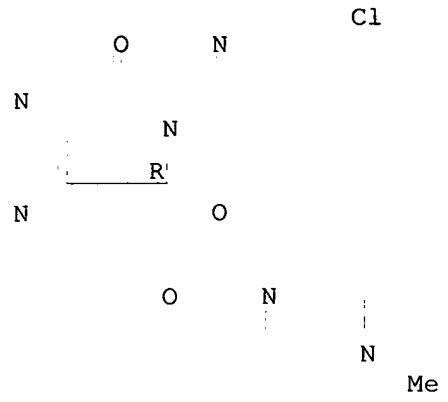

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

24 REFERENCES IN FILE CA (1967 TO DATE)
24 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:55957 Sedative and anxiolytic effects of zopiclone's enantiomers and metabolite. Carlson, J. N.; Haskew, R.; Wacker, J.; Maisonneuve, I. M.; Glick, S. D.; Jerussi, T. P. (Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, NY, 12208, USA). Eur. J. Pharmacol., 415(2,3), 181-189 (English) 2001. CODEN: EJPHAZ. ISSN: 0014-2999. Publisher: Elsevier Science B.V..

AB We evaluated racemic zopiclone, its (S)- and (R)-enantiomers and a metabolite, (S)-desmethylzopiclone, for their actions on locomotor activity, rotarod performance, the elevated plus maze and the Vogel conflict test of anxiety, and electroconvulsive shock-induced seizures duration. Zopiclone and its (R)- and (S)-enantiomers reduced locomotor activity, and zopiclone and its (S)-enantiomer disrupted rotarod performance at 10 mg/kg. (S)-desmethylzopiclone did not alter these measures at doses of less than 200 mg/kg. (S)-desmethylzopiclone altered plus maze performance at the lowest dose of all the zopiclone derivs. tested, caused a dose-related effect on the Vogel conflict test and caused a dose-related redn. of electroconvulsive shock-induced seizure durations. The data indicate that (S)-desmethylzopiclone can bring about an anxiolytic effect without a substantial degree of central nervous system depression, and suggest that the agent may be particularly useful clin. in the treatment of anxiety.

REFERENCE 2: 134:76391 Timed dual release dosage forms comprising a short acting hypnotic or a salt thereof. Alaux, Gerard; Andre, Frederic; Ducassou, Jean; Lewis, Gareth (Sanofi-Synthelabo, Fr.). Eur. Pat. Appl. EP 1064937 A1 20010103, 17 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1999-401605 19990628.

AB The invention relates to timed dual release dosage forms of short acting hypnotics or salts adapted to release the short-acting hypnotic over a predetd. time, according to a profile of dissoln. characterized in that it comprises two release pulses, the first being immediate and the second being delayed by a fixed time. Immediated-release pellets contg. zolpidem hemitartrate were prepd. and coated pellets contg. zolpidem hemitartrate, tartaric acid and benzalkonium chloride prepd. and coated with a Eudragit RS100/RL100 soln.

REFERENCE 3: 134:9361 Methods of making and using N-desmethylzopiclone. Jerussi, Thomas P.; Senanayake, Chrisantha H.; Rubin, Paul D.; Hong,

Yaping; Bakale, Roger A.; Xiang, Tingjian; McConville, Fran A. (Sepracor Inc., USA). PCT Int. Appl. WO 2000069442 A1 20001123, 44 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US12820 20000511. PRIORITY: US 1999-PV134239 19990514; US 1999-PV135037 19990520; US 2000-548607 20000413.

AB The invention is directed to compns. comprising, and methods of using, racemic N-desmethylzopiclone, optically pure (+)-N-desmethylzopiclone, and optically pure (-)-N-desmethylzopiclone in the treatment and prevention of diseases and conditions in mammals. The invention is further directed to novel methods of prepg. N-desmethylzopiclone, optically pure (+)-N-desmethylzopiclone, and optically pure (-)-N-desmethylzopiclone. The compds. are administered to patients suffering from, anxiety, convulsions, depression, behavioral disorders, sleep disorders, etc.

REFERENCE 4: 133:183136 Separation of enantiomers of drugs by capillary electrophoresis with permethyl-gamma-cyclodextrin as chiral solvating agent. Koppenhoefer, Bernhard; Jakob, Andreas; Zhu, Xiaofeng; Lin, Bingcheng (Institute of Organic Chemistry, University of Tubingen, Germany). Journal of High Resolution Chromatography, 23(6), 413-429 (English) 2000. CODEN: JHRCE7. ISSN: 0935-6304. Publisher: Wiley-VCH Verlag GmbH.

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REFERENCE 5: 133:79354 Pharmaceutical composition for oral administration designed to prevent misuse at the expense of a third party. Dufour, Alain; Ahond, Christian (Sanofi-Synthelabo, Fr.). PCT Int. Appl. WO 2000038649 A1 20000706, 35 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (French). CODEN: PIXXD2. APPLICATION: WO 1999-FR3120 19991214. PRIORITY: FR 1998-16309 19981223.

AB The invention concerns a pharmaceutical compn. for oral administration to prevent misuse at the expense of a third party. A three-layer 260 mg oral tablet contg. 15 mg zolpidem hemitartarate (I) in the active layer was prepd. The dissoln. of I was .gtoreq.80% after 15 min.

REFERENCE 6: 133:22433 Controlled-release dosage forms comprising a short acting hypnotic or a salt. Alaux, Gerard; Lewis, Gareth; Andre, Frederic

(Synthelabo S. A., Fr.). Eur. Pat. Appl. EP 1005863 A1 20000607, 24 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 1998-403037 19981204.

AB The present invention relates to controlled-release dosage forms of short acting hypnotics or salts thereof adapted to release the short acting hypnotic over a predetd. time period, according to a biphasic profile of dissoln., where the first phase is an immediate release phase and the second phase is a prolonged release phase. Thus, prolonged-release tablets comprising 10 mg zolpidem hemitartrate were prepd. from zolpidem hemitartrate 8.3, lactose 86.6, citric acid 2.5, HPMC-606 2.1, and Mg stearate 0.5%. Tablets were coated, in a pan coater, with a sufficient quantity of the following mixt. to obtain the desired dissoln. profile: Et cellulose 2.0, di-Et phthalate 0.4, HPMC-606 2.0, isopropanol 47.8, and dichloromethane 47.8%.

REFERENCE 7: 131:277050 Separation of drugs by capillary electrophoresis. Part 10. Permethyl-alpha-cyclodextrin as chiral solvating agent. Zhu, Xiao Feng; Lin, Bing Cheng; Jakob, Andreas; Wuerthner, Stefan; Koppenhoefer, Bernhard (Dalian Inst. Chemical Phys., Dalian, Peop. Rep. China). Electrophoresis, 20(9), 1878-1889 (English) 1999. CODEN: ELCTDN. ISSN: 0173-0835. Publisher: Wiley-VCH Verlag GmbH.

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REFERENCE 8: 130:261430 Stereoselective binding of zopiclone to human plasma proteins. Fernandez, Christine; Gimenez, Francois; Thuillier, Alain; Farinotti, Robert (Hopital Pitie-Salpetriere, Service Pharmacie-Pharmacocinetique, Paris, 75013, Fr.). Chirality, 11(2), 129-132 (English) 1999. CODEN: CHRLEP. ISSN: 0899-0042. Publisher: Wiley-Liss, Inc..

AB The binding of racemic zopiclone (ZOP) and of its two enantiomers to plasma proteins, albumin and .alpha.1-acid glycoprotein were compared. Our work shows that the binding of ZOP to human plasma proteins is stereoselective. The total plasma protein binding percentages were 79.3.+-.5.5%, 83.8.+-.5.2%, and 75.1.+-.2.1%, for racemic zopiclone, (-)-zopiclone and (+)-zopiclone, resp. These results were confirmed by the anal. of samples obtained from healthy volunteers after the oral administration of ZOP. The anticoagulant used for sampling was also shown to have an influence on the percentage binding and on its stereoselectivity. Considering albumin and .alpha.1-acid glycoprotein sep., stereoselectivity was also obsd.

REFERENCE 9: 129:221244 Separation of enantiomers of drugs by capillary electrophoresis, part 7: gamma-cyclodextrin as chiral solvating agent. Koppenhoefer, Bernhard; Epperlein, Ulrich; Jakob, Andreas; Wuerthner, Stefan; Xiaofeng, Zhu; Bingcheng, Lin (Institute for Organic Chemistry, University of Tiibingen, Tuibingen, Germany). Chirality, 10(6), 548-554 (English) 1998. CODEN: CHRLEP. ISSN: 0899-0042. Publisher: Wiley-Liss, Inc..

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1998:466560 Document No. 129:140784 Separation of enantiomers of drugs by capillary electrophoresis. Part 8. .beta.-Cyclodextrin as chiral solvating agent. Lin, B.; Zhu, X.; Wuerthner, S.; Epperlein, U.; Koppenhoefer, B. (Institute of Chemical Physics, Dalian, Peop. Rep. China). Talanta, 46(4), 743-749 (English) 1998. CODEN: TLNTA2. ISSN: 0039-9140. Publisher: Elsevier Science B.V..
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L13 ANSWER 12 OF 30 CAPLUS COPYRIGHT 2002 ACS
1998:562120 Document No. 129:221244 Separation of enantiomers of drugs by capillary electrophoresis, part 7: gamma-cyclodextrin as chiral solvating agent. Koppenhoefer, Bernhard; Epperlein, Ulrich; Jakob, Andreas; Wuerthner, Stefan; Xiaofeng, Zhu; Bingcheng, Lin (Institute for Organic Chemistry, University of Tiibingen, Tuibingen, Germany). Chirality, 10(6), 548-554 (English) 1998. CODEN: CHRLEP. ISSN: 0899-0042. Publisher: Wiley-Liss, Inc..
AB Following an extended chiral drug screening program by capillary zone electrophoresis (CZE), the enantiosepn. of 86 racemic drugs was tested with .gamma.-cyclodextrin as a chiral solvating agent. Unified conditions were applied to all expts. In total, 18 drug racemates were sepd., 13 entries thereof that had not been sepd. at the lower CSA concn. applied in an earlier stage of the project. A comparison of the data with the results obtained for .alpha.- and .beta.-cyclodextrin points to the significance of partial penetration ("side-on binding") of aryl groups into the cyclodextrin cavity.

L13 ANSWER 13 OF 30 CAPLUS COPYRIGHT 2002 ACS
1997:808131 Document No. 128:106484 Separation of enantiomers of drugs by capillary electrophoresis V. Hydroxypropyl-.alpha.-cyclodextrin as chiral solvating agent. Koppenhoefer, Bernhard; Epperlein, Ulrich; Schlunk, Rainer; Zhu, Xiaofeng; Lin, Bingcheng (Auf der Morgenstelle 18, Institute for Organic Chemistry, University of Tubingen, D-72076 Tubingen, Germany). J. Chromatogr., A, 793(1), 153-164 (English) 1998. CODEN: JCRAEY. ISSN: 0021-9673. Publisher: Elsevier Science B.V..
AB In an extended chiral drug screening program, enantiosepn. of 86 racemic drugs was tested with hydroxypropyl-.alpha.-cyclodextrin as chiral solvating agent (CSA). A total of 34 drugs out of 86 could be resolved in this straightforward approach. The no. of expts. performed under identical conditions allows a correlation of the sepn. factors .alpha.m with the interaction strengths Rm. As shown for a subset of 23 drugs, the concn. of the CSA is a crucial parameter for further optimization.

L13 ANSWER 14 OF 30 CAPLUS COPYRIGHT 2002 ACS
1998:169710 Document No. 128:167442 (+)-6-(5-Chloropyrid-2-yl)-7-oxo-5-[[(vinyloxy)carbonyl]oxy]-5,6-dihydropyrrolo[3,4-b]pyrazine and its use in a process for preparation of (+)-6-(5-chloropyrid-2-yl)-5-[[(4-methylpiperazin-1-yl)carbonyl]oxy]-7-oxo-5,6-dihydropyrrolo[3,4-b]pyrazine [(+)-zopiclone]. Gotor Santamaria, Vicente; Brieva Collado, Rosario; Linares Lopez, Francisco J.; Garcia Campos, Roberto; Bayod Jasanada, Miguel Santos (Astupaharma, S.A., Spain). Span. ES 2101653 A1 19970701, 6 pp. (Spanish). CODEN: SPXXAD. APPLICATION: ES 1995-1385 19950710.
GI

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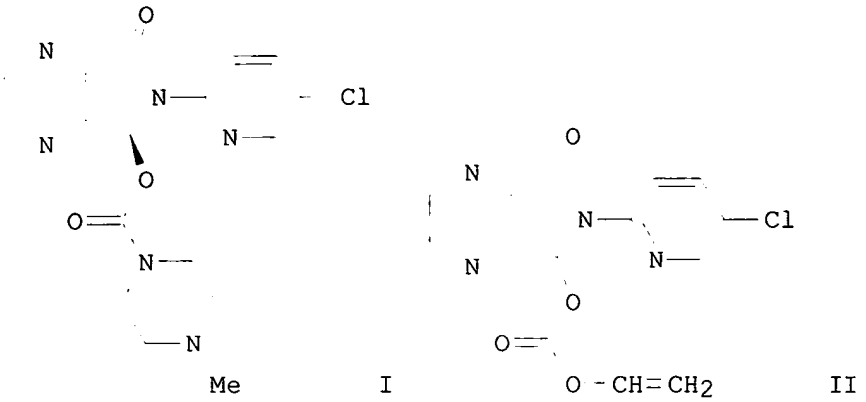
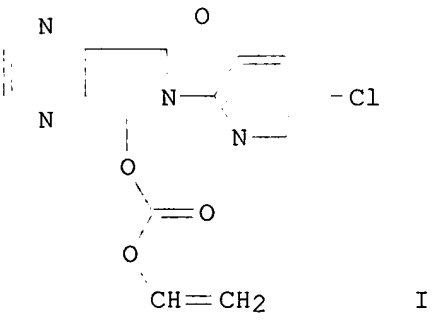


Me I O-CH=CH2 II

AB The hypnotic drug (+)-zopiclone, i.e. (+)-I, is prepd. in 3 steps, under mild conditions and with good yields, via the title intermediate (+)-II. Thus, 6-(5-chloropyrid-2-yl)-5-hydroxy-7-oxo-5,6-dihydropyrrolo[3,4-b]pyrazine was esterified with vinyl chloroformate in pyridine to give II, which was subjected to enzymic resoln. using lipase of Candida antarctica to leave (+)-II with >95% enantiomeric excess (ee). Condensation of the latter with N-methylpiperazine gave (+)-I, also with >95% ee.

L13 ANSWER 15 OF 30 CAPLUS COPYRIGHT 2002 ACS
1997:283156 Document No. 127:17641 Enzymic resolution of (.+-.)-6-(5-chloropyridin-2-yl)-7-vinyloxycarbonyloxy-6,7-dihydro[5H]pyrrolo[3,4-b]pyrazin-5-one. Synthesis of (+)-zopiclone. Gotor, Vicente; Limeres, Fernando; Garcia, Roberto; Bayod, Miguel; Brieva, Rosario (Departmento de Quimica Organica e Inorganica, Facultad de Quimica, Universidad de Oviedo, Oviedo, 33071, Spain). Tetrahedron: Asymmetry, 8(7), 995-997 (English) 1997. CODEN: TASYE3. ISSN: 0957-4166. OTHER SOURCES: CASREACT 127:17641. Publisher: Elsevier.
GI



CH=CH2 I

AB The lipase from Candida antarctica (CAL) catalyzes the resoln. of a precursor of zopiclone, I, through hydrolysis and transcarbonatation processes. I is then reacted with N-methylpiperazine to give (+)-zopiclone.

L13 ANSWER 16 OF 30 CAPLUS COPYRIGHT 2002 ACS
1996:460115 Document No. 125:184730 Semi-preparative chiral resolution of

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zopiclone and N-desmethylzopiclone. Mannaert, Erik; Daenens, Paul (Lab. Toxicol., Katholieke Univ. Leuven, Louvain, B-3000, Belg.). J. Pharm. Biomed. Anal., 14(8-10), 1367-1370 (English) 1996. CODEN: JPBADA. ISSN: 0731-7085.

AB Sepn. of the enantiomers was accomplished by liq. chromatog. using a com. available Chiralpak AS column. The asym. peak shape of (-)-N-desmethylzopiclone in comparison with that of (-)-zopiclone shows that the interaction of stereoisomers with the chiral stationary phase is crit. and often not predictable. Nonetheless, a max. load of 3 mg per injection could be achieved for the N-desmethyl metabolite. In one working week, about 100 mg of the enantiomers of N-desmethylzopiclone and about 50 mg of the enantiomers of zopiclone were collected in a pure state.

L13 ANSWER 17 OF 30 CAPLUS COPYRIGHT 2002 ACS

1996:668647 Document No. 125:339189 Capillary electrophoresis for separation of drug enantiomers using different cyclodextrins as chiral selectors. Ji, Yibing; Chen, Yuying; Lin, Bingchen (Department Analytical Chemistry, China Pharmaceutical University, Nanjing, 210038, Peop. Rep. China). Zhongguo Yaoke Daxue Xuebao, 27(6), 363-365 (Chinese) 1996. CODEN: ZHYXE9. ISSN: 1000-5048.

AB Ten compds. were chirally sepd. by adding .alpha.-, .beta.-, .gamma.-cyclodextrin (CD) as chiral selector, resp. Due to the different cavity sizes, .alpha.-, .beta.-,, .gamma.-CD had different selectivities to the compds. with different sizes and shapes, and the "size-match" principle and complexation between CD and the guest compds. was introduced to explain the exptl. results. The chiral recognition mechanism was further proved.

L13 ANSWER 18 OF 30 CAPLUS COPYRIGHT 2002 ACS

1996:348014 Document No. 125:96309 Separation of enantiomers of drugs by capillary electrophoresis. III. .beta.-cyclodextrin as chiral solvating agent. Koppenhoefer, B.; Epperlein, U.; Christian, B.; Lin, B.; Ji, Y.; Chen, Y. (University of Tuebingen, Auf der Morgenstelle 18, Tubingen, D-72076, Germany). J. Chromatogr., A, 735(1 + 2), 333-343 (English) 1996. CODEN: JCRAEY. ISSN: 0021-9673.

AB Enantiomer sepn. by capillary zone electrophoresis was studied for a set of 34 chiral drugs. Keeping the concn. of .beta.-cyclodextrin as a chiral solvating agent as const. as possible led to the sepn. of 7 enantiomeric pairs. Carvedilol, tetryzoline, tropicamide and zopiclone gave a baseline sepn., chlorphenamine, ketamine, and orciprenaline a partial sepn. Statistical anal. revealed that the best sepn. factors were obsd. for a medium degree of interaction with the cyclodextrin. A theory explaining this effect provides a helpful guideline for further optimization.

L13 ANSWER 19 OF 30 CAPLUS COPYRIGHT 2002 ACS

1996:77010 Document No. 124:193152 Enantioselective determination of zopiclone and its metabolites in urine by capillary electrophoresis. Hempel, G.; Blaschke, G. (Munster, D-48149, Germany). J. Chromatogr., B: Biomed. Appl., 675(1), 139-46 (English) 1996. CODEN: JCBBEP. ISSN: 0378-4347.

AB A method has been developed for the stereoselective detn. of zopiclone and its main metabolites in urine. After the addn. of the internal std. zolpidem the urine samples were extd. at pH 8 with chloroform-isopropanol (9:1). Analyses were carried out using capillary electrophoresis (CE) with .beta.-cyclodextrin as the chiral selector. The analytes were detected using UV laser-induced fluorescence detection with a He-Cd laser operated at 325 nm. Urine samples of two volunteers after oral administration of 7.5 mg zopiclone were investigated. The S-(+)-enantiomers of zopiclone and its metabolites were always excreted in higher amts. than the R-(-)-enantiomers. With the same method the zopiclone enantiomers were quantified in saliva. Compared to

high-performance liq. chromatog., the CE method is very fast and simple.

L13 ANSWER 20 OF 30 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2

1996:479820 Document No.: PREV199699195076. Development of a stereospecific radioimmunoassay for the analysis of zopiclone and metabolites in urine. Mannaert, Erik; Tytgat, Jan; Daenens, Paul (1). (1) Lab. Toxicol., Katholieke Univ. Leuven, E. Van Evenstraat 4, B-3000 Leuven Belgium. Clinica Chimica Acta, (1996) Vol. 253, No. 1-2, pp. 103-115. ISSN: 0009-8981. Language: English.

AB A sensitive and specific radioimmunoassay has been developed, allowing the stereospecific detection of nanogram amounts of (+)- and (-)-enantiomers of zopiclone and its major metabolites in urine, without prior extraction or purification. Antisera were obtained from two series of four rabbits, immunized with optically pure (+)- and (-)-N-hemisuccinyldesmethylzopiclone, conjugated to bovine serum albumin according to the active ester method. The assay was stereospecific, allowing discrimination between the two enantiomers of N-desmethylzopiclone with mutual cross-reactivities below 2%. Substantial cross-reaction was observed with the parent compound, although lower than expected, and to a lesser extent with the N-oxide metabolite. A selection of hypnotics, anxiolytics, antidepressants and some other widely used drugs did not interfere with the assay (lt 0.1%), when tested at a concentration level of 10 mu-g/ml. The sensitivity of the assay was 50 pg/ml and 10 pg/ml for the (+)- and (-)-enantiomers, respectively. The binding assay described here was used to evaluate the stereoselective excretion pattern of zopiclone. Analysis of cumulative excretion samples from a volunteer revealed a mean metabolic excretion ratio (+)/(-) of 2.2, ranging from 1.7 (7 h) to 4.4 (36 h). A mean excretion ratio (+)/(-) of 2.5 +- 1 was calculated after analysis of urine samples from 20 patients receiving zopiclone as a hypnotic daily.

L13 ANSWER 21 OF 30 CAPLUS COPYRIGHT 2002 ACS

1995:713029 Document No. 123:132685 Degradation and racemization of zopiclone enantiomers in plasma and partially aqueous solutions. Fernandez, Christina; Gimenez, Francois; Mayrargue, Joelle; Thuillier, Alain; Farinotti, Robert (Service Pharmacie, Hopital Pitie-Salpetriere, Paris, Fr.). Chirality, 7(4), 267-71 (English) 1995. CODEN: CHRLEP. ISSN: 0899-0042.

AB We investigated the degrdn. and racemization zopiclone (ZOP) enantiomers in plasma and partially aq. solns. (ethanol:phosphate buffer). Degrdn. and racemization increased with increasing pH and temp. Degrdn. products were identified by means of mass spectrometry, which revealed hydrolysis of the carbamate function and opening of the pyrrolidone ring. In plasma, neither degrdn. nor racemization occurred after 6 mo of storage at -20.degree.C and subsequent extn.

L13 ANSWER 22 OF 30 CAPLUS COPYRIGHT 2002 ACS

1995:713028 Document No. 123:123299 Solvent selectivity in chiral chromatography using a .beta.-cyclodextrin-bonded phase. Piperaki, Stavroula; Tsantili-Kakoulidou, Anna; Parissi-Poulou, Maria (Dep. Pharmacy, Univ. Athens, Athens, Greece). Chirality, 7(4), 257-66 (English) 1995. CODEN: CHRLEP. ISSN: 0899-0042.

AB A .beta.-cyclodextrin-bonded phase has been used to investigate the sepn. of the enantiomers of atenolol, oxprenolol, celiprolol, tertatolol, terbutaline, fluoxetine, norfluoxetine, and zopiclone, focusing on the importance of solvent selectivity. With cyclodextrin (CD)-bonded phases, chiral discrimination occurs because the two enantiomers of a racemate form inclusion complexes of different strengths within the CD cavity. The org. modifier mols. tend to compete with solutes for a definite no. of adsorption sites on the stationary phase. Moreover, the ternary complex formation may play an important role in chiral recognition. In this study, it was of interest to est. the influence of mobile phase modifiers

with respect to solvent type (i.e., MeCN, MeOH, EtOH, THF, i-PrOH, PrOH and t-BuOH), size and shape, and concns. Solvent selectivity has been investigated by using different org. modifiers in mobile phases with the same polarity, and relationships were established between the logarithm of solvent partition coeff. (log P2) and the three most important chromatog. parameters: retention time (t), resoln. (R), and enantioselectivity (.alpha.). Thus, it seems that they hydrophobicity of the org. modifier becomes one of the dominant factors affecting the inclusion process phenomena. Further, the apparent partition coeffs. of the compds. under study have been detd. and a comparison has been attempted regarding the degree of their enantiomeric resoln.

L13 ANSWER 23 OF 30 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1995:6623 Document No.: PREV199598020923. Pharmacokinetics (PK) of zopiclone (ZPC) enantiomers in humans following oral dose administration of racemate. Foster, Robert T. (1); Caille, Gilles; Ngoc, Anh Ho; Lemko, Cathy H. (1); Kherani, Raheem (1); Pasutto, Franco M. (1). (1) Fac. Pharmacy, University Alberta, Edmonton, AB Canada. Pharmaceutical Research (New York), (1994) Vol. 11, No. 10 SUPPL., pp. S402. Meeting Info.: Ninth Annual Meeting of the American Association of Pharmaceutical Scientists San Diego, California, USA November 6-10, 1994 ISSN: 0724-8741. Language: English.

L13 ANSWER 24 OF 30 CAPLUS COPYRIGHT 2002 ACS
1994:594792 Document No. 121:194792 Stereospecific high-performance liquid chromatographic assay of zopiclone in human plasma. Foster, Robert T.; Caille, Gilles; Ngoc, Anh Ho; Lemko, Cathy H.; Kherani, Raheem; Pasutto, Franco M. (Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, T6G 2N8, Can.). J. Chromatogr., B: Biomed. Appl., 658(1), 161-6 (English) 1994. CODEN: JCBBEP.
AB A high-performance liq. chromatog. (HPLC) assay for the anal. of the enantiomers of zopiclone (ZPC), a cyclopyrrolone hypnotic, in plasma was developed. Following the addn. of chlordiazepoxide as internal std. (I.S.), plasma contg. the ZPC enantiomers and I.S. was extd. by liq.-liq. extn. at an alk. pH. After evapn. of the org. layer, the drug and I.S. were reconstituted in ethanol-hexane (80:20, vol./vol.) and injected onto the HPLC column. The enantiomers were sepd. at ambient temp. on a 25-cm Chiralcel OD-H column with ethanol-hexane (60:40, vol./vol.) as the mobile phase pumped at a flow-rate of 0.6 mL/min. The enantiomers of ZPC were quantified by fluorescence detection with excitation and emission wavelengths of 300 and 470 nm, resp. The assay described allows for the direct quantitation of ZPC without pre-column derivatization, and is suitable for clin. studies of ZPC in humans after administration of therapeutic doses.

L13 ANSWER 25 OF 30 CAPLUS COPYRIGHT 2002 ACS
1993:463060 Document No. 119:63060 Treating sleep disorders, convulsive seizure, and other disorders using optically pure (-)-zopiclone. Young, James W.; Brandt, Steven (Sepracor, Inc., USA). PCT Int. Appl. WO 9310788 A1 19930610, 41 pp. DESIGNATED STATES: W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, UA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US10705 19921201. PRIORITY: US 1991-801313 19911202.
AB (-)-Zopiclone (I) is a drug for treatment of sleep disorders and convulsive disorders. I is free of the side effects of (.+-.)-zopiclone. I is also useful for treating disorders affected by the agonist binding to central nervous system benzodiazepine receptors, such as anxiety and aggressive behavior.

L13 ANSWER 26 OF 30 CAPLUS COPYRIGHT 2002 ACS
1993:463059 Document No. 119:63059 Treating sleep disorders, convulsive

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seizures, and other disorders using optically pure (+)-zopiclone. Young, James W.; Brandt, Steven (Sepracor, Inc., USA). PCT Int. Appl. WO 9310787 A1 19930610, 41 pp. DESIGNATED STATES: W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, UA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US10631 19921201. PRIORITY: US 1991-801312 19911202.

AB (+)-Zopiclone (I) is effective in treating sleep disorders and convulsive disorders. I is free of the side effects of (.+-.)-zopiclone. I is also useful for treating disorders affected by the agonist binding to central nervous system or peripheral benzodiazepine receptors.

L13 ANSWER 27 OF 30 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3

1994:66551 Document No.: PREV199497079551. Pharmacokinetics of zopiclone and its enantiomers in Caucasian young healthy volunteers. Fernandez, C.; Maradeix, V.; Gimenez, F. (1); Thuillier, A.; Farinotti, R.. (1) Hopital Pitie-Salpetriere, Pharmacie, 47 Boulevard de l'Hopital, 75651 Paris Cedex 13 France. Drug Metabolism and Disposition, (1993) Vol. 21, No. 6, pp. 1125-1128. ISSN: 0090-9556. Language: English.

AB The disposition of the enantiomers of zopiclone and its two chiral metabolites was investigated after oral administration of a single dose of 15 mg of a racemic mixture (twice the usual therapeutic regimen) in 12 adult Caucasian volunteers. Determination of concentrations of zopiclone enantiomers in plasma showed that zopiclone pharmacokinetics is stereoselective with AUC-0 fwdarw - infin values of 691.3 and 209.5 ng cntdot ml-1 cntdot hr (p lt 0.001), C-max values of 87.3 and 44.0 ng cntdot ml-1 (p lt 0.001), oral CL-tot/F values of 195.5 and 659.8 ml cntdot min-1 (p lt 0.001), Vd/F values of 98.6 and 192.8 liters (p lt 0.01) and elimination half-life of 399.2 and 225.6 min (p lt 0.01) for (+)-zopiclone and (-)-zopiclone, respectively. On the contrary, absorption half-life and T-max values were not significantly different. In 48-hr urine, 3.6% of unchanged zopiclone was excreted, whereas 14.2% and 13.8% of both metabolites, N-desmethylzopiclone and N-oxidezopiclone, respectively, were found. Quantities of (+)-zopiclone excreted in urine were always higher compared with its antipode (-)-zopiclone for the 12 volunteers (p lt 0.001). For the metabolites, quantities of both enantiomers were either equal or different and when different, it was always in favor of the (+)-enantiomer.

L13 ANSWER 28 OF 30 CAPLUS COPYRIGHT 2002 ACS

1994:22978 Document No. 120:22978 Determination of the enantiomers of zopiclone and its two chiral metabolites in urine using an automated coupled achiral-chiral chromatographic system. Fernandez, Christine; Gimenez, Francois; Baune, Bruno; Maradeix, Valerie; Thuillier, Alain (Serv. Pharm., Hop. Pitie Salpetriere, Paris, 75013, Fr.). J. Chromatogr., Biomed. Appl., 617(2), 271-8 (English) 1993. CODEN: JCBADL. ISSN: 0378-4347.

AB The enantiomers of zopiclone and its two chiral N-desmethyl and N-oxide metabolites were detd. in urine using a coupled achiral-chiral liq. chromatog. method. After liq.-liq. extn., zopiclone and its two metabolites were quantified on a cyanopropyl column. After fluorimetric detection on the achiral system, the eluent was switched through a silica precolumn in order to trap and conc. the analytes. Each fraction was then backflushed sep. onto a carbamate cellulose chiral stationary phase in order to det. the enantiomeric ratios. The coupled system was automated with an autosampler and a switching value programmed by an integrator. The method was validated, and a first trial was performed on urine samples of a volunteer treated with 15 mg of racemic zopiclone.

L13 ANSWER 29 OF 30 CAPLUS COPYRIGHT 2002 ACS

1992:591870 Document No. 117:191870 Preparation of (-)-zopiclone. Cotrel,

Claude; Roussel, Gerard (Rhone-Poulenc Rorer S. A., Fr.). Eur. Pat. Appl. EP 495717 A1 19920722, 5 pp. DESIGNATED STATES: R: PT. (French). CODEN: EPXXDW. APPLICATION: EP 1992-400111 19920116. PRIORITY: FR 1991-490 19910117.

AB The title compd., prepd. by optical resoln. of racemic zopiclone as the D-(+)-O,O'-dibenzolyltartrate salt, is about twice as active as the racemate and had LD50 of .apprx.1.5 g/kg orally in mice.

L13 ANSWER 30 OF 30 CAPLUS COPYRIGHT 2002 ACS

1992:75574 Document No. 116:75574 Determination of zopiclone enantiomers in plasma by liquid chromatography using a chiral cellulose carbamate column. Fernandez, Christine; Baune, Bruno; Gimenez, Francois; Thuillier, Alain; Farinotti, Robert (Serv. Pharm., Hop. Pitie Salpetriere, Paris, 75013, Fr.). J. Chromatogr., 572(1-2), 195-202 (English) 1991. CODEN: JOCRAM. ISSN: 0021-9673.

AB The enantiomers of zopiclone were detd. in human plasma using a sequential achiral-chiral liq. chromatog. method. Zopiclone was sepd. from the biol. matrix and quantified on an achiral silica column. The limit of detection was 5 ng/mL. The eluent fraction contg. zopiclone was collected, evapd., reconstituted with the mobile phase and injected onto a chiral cellulose carbamate column where the enantiomeric ratio was calcd. This validated method, applied to a pilot study, suggests that pharmacokinetics of zopiclone is stereoselective.

=> fil reg;e zopiclone/cn 5

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E1            1     ZOPFINOL/CN
E2            1     ZOPHREN/CN
E3            1 --> ZOPICLONE/CN
E4            1     ZOPICLONE N-OXIDE/CN
E5            1     ZOPOLRESTAT/CN

=> s e3;d ide can
L14           1 ZOPICLONE/CN
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L14  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   43200-80-2  REGISTRY
CN   1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-
     dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   5H-Pyrrolo[3,4-b]pyrazine, 1-piperazinecarboxylic acid deriv.
OTHER NAMES:
CN   (.+-.)-Zopiclone
CN   Imovane
CN   RP 27267
CN   Zopiclone
FS   3D CONCORD
DR   138680-07-6
MF   C17 H17 Cl N6 O3
CI   COM
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
       BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB,
       CEN, CHEMCATS, CHEMLIST, CIN, DDFU, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES,
       EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC,
       PHAR, PHARMASEARCH, PROMT, RTECS*, SYNTHLINE, TOXCENTER, TOXLIT, USAN,
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         (**Enter CHEMLIST File for up-to-date regulatory information)
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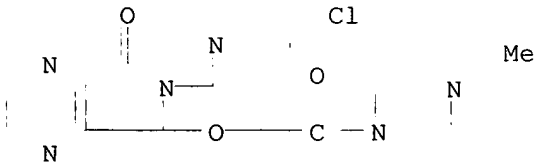

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              6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
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REFERENCE 3: 136:16116

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REFERENCE 8: 135:220641

REFERENCE 9: 135:205436

REFERENCE 10: 135:174433

=> fil medl,caplus,biosis,embase,jicst;s (l14 or zopiclone?)(10a)("d" or "l" or "s" or "r")

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TOTAL FOR ALL FILES
L20 97 (L14 OR ZOPICLONE?)(10A)("D" OR "L" OR "S" OR "R")

=> s l20 and range=(,1991)
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Operators must be followed by a search term, L-number, or query name.

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      (FILE 'HOME' ENTERED AT 12:25:58 ON 21 FEB 2002)

      FILE 'REGISTRY' ENTERED AT 12:26:05 ON 21 FEB 2002
L1              STR
L2            1 S L1
L3              STR L1
L4           12 S L3 FUL
L5            0 S L4(L)("D" OR "L" OR "S"OR "R")/CN
L6            6 S L4(L)("D" OR "L" OR "S"OR "R")

      FILE 'BIOSIS, CAPLUS, MEDLINE, JICST-EPLUS, EMBASE' ENTERED AT 12:33:20
      ON 21 FEB 2002
L7            4 FILE BIOSIS
L8           29 FILE CAPLUS
L9            0 FILE MEDLINE
L10           0 FILE JICST-EPLUS
L11           0 FILE EMBASE
      TOTAL FOR ALL FILES
L12          33 S L6
L13          30 DUP REM L12 (3 DUPLICATES REMOVED)

      FILE 'REGISTRY' ENTERED AT 12:34:23 ON 21 FEB 2002
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L14           1 S E3

      FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, JICST-EPLUS' ENTERED AT 12:35:32
      ON 21 FEB 2002
L15          23 FILE MEDLINE
L16          24 FILE CAPLUS
L17          20 FILE BIOSIS
L18          27 FILE EMBASE
L19           3 FILE JICST-EPLUS
      TOTAL FOR ALL FILES
L20          97 S (L14 OR ZOPICLONE?)(10A)("D" OR "L" OR "S" OR "R")

=> s l20 not l12
L21          23 FILE MEDLINE
L22          17 FILE CAPLUS
L23          20 FILE BIOSIS
L24          27 FILE EMBASE
L25           3 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L26          90 L20 NOT L12

=> dup rem l26
PROCESSING COMPLETED FOR L26
L27           50 DUP REM L26 (40 DUPLICATES REMOVED)

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L28           7 FILE CAPLUS
L29           7 FILE BIOSIS
L30          12 FILE EMBASE
L31           3 FILE JICST-EPLUS


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TOTAL FOR ALL FILES
L32 29 L22

=> dup rem l32
PROCESSING COMPLETED FOR L32
L33 19 DUP REM L32 (10 DUPLICATES REMOVED)

=> d 1-19 cbib abs hit;s l26 not l32

L33 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
1991:422119 Document No. 115:22119 Involvement of the dorsal hippocampus in mediation of the antianxiety action of tandospirone, a 5-hydroxytryptaminelA agonistic anxiolytic. Kataoka, Y.; Shibata, K.; Miyazaki, A.; Inoue, Y.; Tominaga, K.; Koizumi, S.; Ueki, S.; Niwa, M. (Sch. Med., Nagasaki Univ., Nagasaki, 852, Japan). Neuropharmacology, 30(5), 475-80 (English) 1991. CODEN: NEPHBW. ISSN: 0028-3908.
AB The effect of tandospirone, a 5-hydroxytryptamine (5-HT)1A agonist/anxiolytic, injected directly into dorsal hippocampus, on Vogel-type conflict behavior in rats was investigated and the findings were compared with the effects of diazepam and zopiclone. Tandospirone (30 .mu.g/2 .mu.L and 60 .mu.g/2 .mu.**L**) and diazepam (40 .mu.g/2 .mu.**L**) but not **zopiclone** (20 .mu.g/2 .mu.**L**), produced a potent anticonflict action in rats. The anticonflict action of tandospirone (30 .mu.g/2 .mu.L), injected into the dorsal hippocampus, was significantly blocked by (-)-propranolol (5 mg/kg i.p.). The present findings provide evidence that suggests that tandospirone has an antianxiety action, presumably by stimulating 5-HT1A receptors in the dorsal hippocampus.
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L33 ANSWER 2 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
91348473 EMBASE Document No.: 1991348473. Effects of buspirone and other anxiolytics on punished key-pecking in the pigeon. Nanry K.P.; Howard J.L.; Pollard G.T.. Pharmacology Division, Burroughs Wellcome Co.,Research Triangle Park, NC, United States. Drug Development Research 24/3 (269-276) 1991.
ISSN: 0272-4391. CODEN: DDREDK. Pub. Country: United States. Language: English. Summary Language: English.
AB Pigeons were trained to peck a key on a multiple schedule of reinforcement in which 30 responses in the presence of a white cue light produced 3 sec of access to food, and 30 responses in the presence of a red cue light produced 3 sec of access to food and an electric shock, which suppressed responding. Intramuscular injection of the sedative-hypnotic anxiolytics chlordiazepoxide (0.3-10 mg/kg), alprazolam (0.1-3.0 mg/kg), and zopiclone (10-100 mg/kg) substantially increased punished responding. The nonsedative anxiolytics buspirone (0.1-3.0 mg/kg) and ipsapirone (1.0 and 3.0 mg/kg) increased punished responding as much as did the sedative-hypnotics. Buspirone had similar effects in benzodiazepine-naive and benzodiazepine-experienced pigeons. Chlorpromazine (tested at 1-30 mg/kg) and imipramine (tested at 1-30 mg/kg) only decreased unpunished responding at high doses. These results show that (1) the antipunishment

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effects of buspirone and ipsapirone in the pigeon are replicable in another laboratory, (2) buspirone's effect occurs in benzodiazepine-experienced pigeons, and (3) alprazolam and **zopiclone** have antipunishment effects in the pigeon.

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L33 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2

1990:446162 Document No.: BA90:96802. THE EXCRETION OF ZOPICLONE INTO BREAST MILK. MATHESON I; SANDE H A; GAILLOT J. DEP. PHARMACOTHERAPEUTICS, P.O. BOX 1065-BLINDERN, N-0316 OSLO 3, NORWAY.. BR J CLIN PHARMACOL, (1990) 30 (2), 267-272. CODEN: BCPHBM. ISSN: 0306-5251. Language: English.

AB 1. The excretion of zopiclone into breast milk was studied in 12 lactating women in the early postpartum period following the oral administration of a single zopiclone tablet (7.5 mg). 2. The milk/plasma AUC ratio of **zopiclone** was 0.51 .+-. 0.09 (mean .+-. **s.d.**). Individual mean milk/plasma concentration ratios of **zopiclone** showed significant interindividual variation (range 0.41 - 0.70). 3. A comparison of pharmacokinetic parameters in the postpartum women with those reported previously in non-pregnant women, showed significantly higher Cmax values in the lactating mothers; tmax occurred later in milk than in maternal plasma. 4. Assuming a daily milk intake of 0.15 **l** kg-1 and 100% absorption the average infant dose of **zopiclone** in milk would be 1.4% of the weight adjusted dose ingested by the mother.

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L33 ANSWER 4 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

90121625 EMBASE Document No.: 1990121625. [P.**R.** prolongation during voluntary **zopiclone** intoxication]. BLOC AURICULO-VENTRICULAIRE DU 1(ER) DEGRE LORS **D'UNE** INTOXICATION VOLONTAIRE PAR LA **ZOPICLONE**. Regouby Y.; Delomez G.; Tisserant A.. Service de Medecine Polyvalente, Centre Hospitalier de Secteur, B.P. 60, 43100 Brioude, France. Therapie 45/2 (162) 1990. ISSN: 0040-5957. CODEN: THERAP. Pub. Country: France. Language: French.

TI [P.**R.** prolongation during voluntary **zopiclone**

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intoxication].
BLOC AURICULO-VENTRICULAIRE DU 1(ER) DEGRE LORS D'UNE INTOXICATION VOLONTAIRE PAR LA **ZOPICLONE**.

L33 ANSWER 5 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3

1990:418701 Document No.: BA90:79502. COMPARISON OF ZOPICLONE AND FLUNITRAZEPAM IN THE TREATMENT OF INSOMNIA IN DEPRESSED PATIENTS. VAN MOFFAERT M; WILMOTTE J; MESTERS P; VAN WETTERE J P; CABRI C; POELS R. DEP. PSYCHIATRY, UNIV. GHENT, GHENT.. CURR THER RES CLIN EXP, (1990) 48 (1), 140-153. CODEN: CTCEA9. ISSN: 0011-393X. Language: English.

AB The effect and tolerability of 7.5-mg zopiclone were compared with those of 2-mg flunitrazepam over five consecutive days after a two-day placebo washout period. The population study including depressed patients with insomnia who were under treatment with a recently started antidepressant, amitriptyline. After the initial two-day placebo washout period, placebo treatment had already achieved good overall results in both treatment groups, as most of the sleep parameters were significantly improved. However, morning disposition was significantly different between groups and favored zopiclone. Placebo medication was very well tolerated in both groups. At the end of the trial, both zopiclone and flunitrazepam significantly improved sleep onset latency, sleep quality, sleep duration, frequency of nocturnal awakenings, as well as the general evaluation. Although flunitrazepam also significantly improved morning disposition, there was no significant difference between the two treatment groups for any of the sleep parameters. Zopiclone and flunitrazepam achieved a favorable global judgement from the investigator in 66% and 65% of the cases, respectively. About 75% of the patients treated with zopiclone considered the therapeutic results successful compared with only about 60% of patients treated with flunitrazepam. Improvement of vigilance was statistically significant with zopiclone, whereas it was not so with flunitrazepam. Mood at awakening was significantly better in both treatment groups. Investigator's global safety assessment following active treatment significantly favored **zopiclone** over flunitrazepam, since successful results were obtained in 95% versus 74% of the cases. In conclusion, zopiclone is an effective and well-tolerated hypnotic drug in depressed patients undergoing recently started antidepressive treatment. The results achieved with zopiclone were comparable to flunitrazepam.

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L33 ANSWER 6 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1988:313924 Document No.: BA86:30962. EFFECT OF HYPNOTIC DRUGS ON THE DESYNCHRONIZATION OF SLEEP-WAKE RHYTHMS. WATANABE H. DEPARTMENT PSYCHIATRY, TEIKYO UNIVERSITY SCHOOL MEDICINE, JAPAN.. PSYCHIATR NEUROL JPN, (1988) 90 (1), 20-36. CODEN: SSHZAS. ISSN: 0371-2958. Language: Japanese.

AB Change of various sleep parameters associated with desynchronization of sleep-wake circadian rhythm due to the shifts of sleep onset was studied using polysomnography in six healthy volunteers. Subjects were instructed to sleep six hours ealier (advanced shift), or six hours later (delayed shift) than their usual schedule. At advanced shift (A-shift), % stage 3+4 showed no remarkable change, % stage REM decreased and non-REM/REM ratio increased significantly. On the contrary, % stage 3+4 decreased, % stage REM increased and non-REM/REM ratio significantly decreased at delayed shift (**D**-shift). The effects of our four hypnotic drugs (**zopiclone** 10 mg, flunitrazepam 1 mg, triazolam 0.25 mg and levomepromazine 5 mg) and placebo on the desynchronized sleep patterns at A-shift and D-shift were investigated. Drugs or placebo was administered orally thirty minutes before sleep. All drugs prolonged total sleep time and increased sleep efficiency index at A-shift and D-shift. Non-REM/REM ratio at A-shift with triazolam and levomepromazine and distribution of sleep stages at A-shift with levomepromazine resumed to the condition of usual night sleep. Preferable change of non-REM/REM ratio was recognized with all drugs at D-shift, although the effect of levomepromazine was slightly inferior. It is suggested that characteristics of both pharmacological properties of hypnotic drugs and desynchronized sleep patterns should be carefully considered on using hypnotic drugs for sleep-wake schedule disorders.

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L33 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2002 ACS
1988:87973 Document No. 108:87973 Behavioral pharmacology of zopiclone. Ueki, S. (Fac. Pharm. Sci., Kyushu Univ., Fukuoka, Japan). Sleep (N. Y.), 10(Suppl. 1), 1-6 (English) 1987. CODEN: SLEED6. ISSN: 0161-8105.

AB The pharmacol. properties of **zopiclone** (**R** 27267), a

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cyclopyrrolone deriv., were studied in comparison with diazepam, nitrazepam, and flurazepam, on behavioral tests in mice and rats, including open-field activity, Skinner box conflict test, hyperemotionality, and muricidal behavior of olfactory bulbectomized or raphectomized rats, pentetrazole or electroshock convulsions, inclined screen, rotarod, and thiopental-, ether-, or ethanol-induced anesthesia. Zopiclone exhibited pharmacol. properties qual. similar to those of benzodiazepines esp. in conflict, aggressivity, and pentetrazole-induced convulsion tests. On the other hand, its myorelaxant activity was somewhat weaker than that of the ref. drugs. The pharmacol. effects of zopiclone were of short duration.

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L33 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 4

1986:400503 Document No. 105:503 Neuroanatomical site of the inhibitory influence of anxiolytic drugs on central serotonergic transmission. Nishikawa, Toru; Scatton, Bernard (Biochem. Group, Lab. Etud. Rech. Synthelabo, Bagneux, 92220, Fr.). Brain Res., 371(1), 123-32 (English) 1986. CODEN: BRREAP. ISSN: 0006-8993.

AB The neuroanatomical site of the inhibitory influence of anxiolytics on central serotonergic transmission was investigated in the rat by studying the effect of systemic or intracerebral administration of these drugs on cerebral serotonin (5-HT) [50-67-9] synthesis. Systemic administration of diazepam [439-14-5] (3 mg/kg, s.c.) or flunitrazepam [1622-62-4] (1 mg/kg, s.c.) caused a redn. of 5-HT synthesis (as measured by the accumulation of 5-hydroxytryptophan after inhibition of arom. amino acid decarboxylase [9042-64-2]) in the hippocampus but not in the cerebral cortex, striatum, cerebellum or spinal cord of the rat. **Zopiclone** [**43200-80-2**] (22 mg/kg, **s**.c.) decreased the amine synthesis in hippocampus, striatum and prefrontal cortex. The decrease of hippocampal 5-HT synthesis induced by diazepam (5 mg/kg, s.c.) was antagonized by the benzodiazepine antagonist Ro 15-1788 (2 .times. 30 mg/kg, s.c.) but not by the GABA receptor antagonist bicuculline (2 .times. 1 mg/kg, s.c.). Acute cerebral hemitransection or electrolytic lesion of the fasciculus retroflexus did not prevent the ability of diazepam (5 mg/kg, i.p.) to diminish hippocampal 5-HT synthesis. Local infusion of diazepam (15 .mu.g) of flurazepam (1.5 .mu.g) into the hippocampus of conscious rats (via indwelling cannulae) markedly reduced 5-HT synthesis in this brain area whereas infusion of these drugs into the raphe medianus (origin of the serotonergic afferents to the hippocampus) failed to affect hippocampal 5-HT synthesis. In contrast, local injection of muscimol [2763-96-4] (25-150 ng) into the raphe medianus reduced 5-HT synthesis in the hippocampus. This effect of muscimol was potentiated by a systematic administration of diazepam or an intra-raphe medianus infusion of flurazepam (at doses or concns. which exhibited no intrinsic activity). It is concluded from these data that anxiolytic drugs exert an inhibitory influence on hippocampal serotonergic neurons which is mediated primarily via GABA-independent benzodiazepine receptors located in the vicinity of serotonergic nerve terminals.

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L33 ANSWER 9 OF 19 JICST-EPlus COPYRIGHT 2002 JST
860310476 Effectiveness of **Zopiclone** (27 267 **R**.P.) in insomnia. Multi-center double-blind study in comparison with Flurazepam. The second report.. KOBAYASHI RYOZO; HIRABAYASHI YOSHITO; KAZAWA TETSUSHI; YAMASHITA ITARU; ITO KOZO; YASUDA MOTOJI; MURATA TADAYOSHI; TANABE MASAKAZU; YOSHIMURA YOKICHI. Sapporo National Hospital; Keiaikaisapporohanazonobyoin; Sapporotenshibyoin; Hokkaido Univ., School of Medicine, Hospital; Keimeikaishikotsukobyoin; Ishiyamabyoin. Rinsho Hyoka (Clinical Evaluation). (1986) vol. 14, no. 1, pp. 77-108. Journal Code: Y0656A (Fig. 1, Tbl. 18, Ref. 8) CODEN: 0300-3051; Pub. Country: Japan. Language: Japanese.
TI Effectiveness of **Zopiclone** (27 267 **R**.P.) in insomnia. Multi-center double-blind study in comparison with Flurazepam. The second report.

L33 ANSWER 10 OF 19 JICST-EPlus COPYRIGHT 2002 JST
850267339 Effectiveness of a new hypnotic 27 267 **R**.P. (**zopiclone**) on the preoperative night sleep.. OKADA KAZUO; MUTEKI GOSUKE; ISHIDA HIROATSU; MIYAZAKI MASAO; KIYONO SEIICHI; KOBAYASHI KEN'ICHI. Teikyo Univ., School of Medicine; Kurume Univ., Faculty of Medicine; Hyogo College of Medicine; Kyoto Prefect. Univ. of Medicine; Shinshu Univ., Faculty of Medicine; Jikei Univ. School of Medicine. Yakuri to Chiryo (Japanese Pharmacology & Therapeutics). (1985) vol. 13, no. 3, pp. 1667-1674. Journal Code: Z0947A (Fig. 1, Tbl. 14, Ref. 18) CODEN: 0386-3603; Pub. Country: Japan. Language: Japanese.
TI Effectiveness of a new hypnotic 27 267 **R**.P. (**zopiclone**) on the preoperative night sleep.

L33 ANSWER 11 OF 19 JICST-EPlus COPYRIGHT 2002 JST
850404585 Effectiveness of **Zopiclone** (27 267 **R**.P.) in insomnia. Multi-center double-blind study in comparison with Flurazepam.. KOBAYASHI RYOZO; HIRABAYASHI YOSHITO; ITO KOZO; MURATA TADAYOSHI; KAZAWA TETSUSHI; YAMASHITA ITARU; ASANO YUTAKA; IKEDA AKIHO; INAZU MASAYA.

Searched by: Mary Hale 308-4258 CM-1 12D16

Sapporo National Hospital; Keiaikaisapporohanazonobyoin; Sapporotenshibyoin; Hokkaido Univ., School of Medicine, Hospital; Muroransogobyoinshukutsubun'in; Asahikawaidaii Byoin; Iwamizawa Municipal General Hospital. Rinsho Hyoka (Clinical Evaluation). (1985) vol. 13, no. 1, pp. 19-51. Journal Code: Y0656A (Fig. 1, Tbl. 22, Ref. 5) CODEN: 0300-3051; Pub. Country: Japan. Language: Japanese.

TI Effectiveness of **Zopiclone** (27 267 **R**.P.) in insomnia. Multi-center double-blind study in comparison with Flurazepam.

L33 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5

1984:203421 Document No. 100:203421 Chronic oral toxicity tests of **zopiclone** (27 267 **R**.P.) in beagles for 6 months and recovery tests after the treatment. Tamura, Hiroshi; Tsunemi, Kunihiko; Honma, Norio; Haruta, Koichi; Hara, Hideaki; Otaki, Kiyoshi; Marutani, Kiyoshi; Deki, Toshiaki; Karasawa, Inaho; et al. (Ina Res. lab., C.S.K. Lab. Anim. Co., Ltd., Nagano, 399-46, Japan). Oyo Yakuri, 26(6), 969-1003 (Japanese) 1983. CODEN: OYYAA2. ISSN: 0369-8033.

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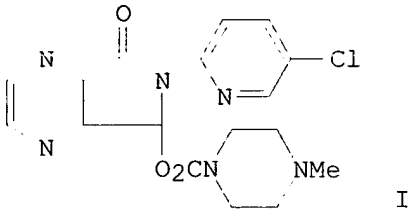

I

AB The chronic toxicity of zopiclone (I) [43200-80-2] was detd. in beagle dogs given 5-25 mg/kg/day for 6 mo. The max. nontoxic dose of I appeared to be 5 mg/kg/day, since some of the dogs given 10-25 mg/kg/day died due to fatal convulsive seizures. I appeared to affect blood cells, blood biochem, bone marrow, and organ wt.

TI Chronic oral toxicity tests of **zopiclone** (27 267 **R**.P.) in beagles for 6 months and recovery tests after the treatment

L33 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6

1984:185348 Document No. 100:185348 Subacute oral toxicity tests of **zopiclone** (27 267 **R**.P.) in beagles for one month and recovery tests after the treatment. Tamura, Hiroshi; Tsunemi, Kunihiko; Haruta, Koichi; Hara, Hideaki; Otaki, Kiyoshi; Deki, Toshiaki; Uchiyama, Tomoharu; Otani, Takehiko (Ina Res. Lab., C.S.K. Lab. Anim. Co., Ltd., Nagano, 399-46, Japan). Oyo Yakuri, 26(6), 943-68 (Japanese) 1983. CODEN: OYYAA2. ISSN: 0369-8033.

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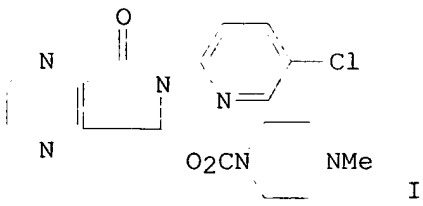

I

AB Extensive biochem. and pathol. studies on beagles receiving various oral doses of zopiclone (I) [43200-80-2] daily for 1 mo, followed by a 2-wk

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recovery period, indicated that 5 mg/kg/day was the max. dose which caused no observable effects at all and that 25 mg/kg/day was the max. safe dose.

TI Subacute oral toxicity tests of **zopiclone** (27 267 **R**.P.) in beagles for one month and recovery tests after the treatment

L33 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 7

1984:203420 Document No. 100:203420 Acute toxicity of **zopiclone** (27 267 **R**.P.) in mice and rats. Nakamura, Katsumi; Deki, Toshiaki; Nakagawa, Tsuguo; Higo, Shinichiro; Sakamaki, Yoshiyuki; Kasuga, Yoshitomo; Tsurukawa, Koichi; Uchiyama, Tomoharu; Otani, Takehiko (Ina Res. Lab., C.S.K. Lab. Anim. Co., Ltd., Nagano, 399-46, Japan). Oyo Yakuri, 26(6), 935-41 (Japanese) 1983. CODEN: OYYAA2. ISSN: 0369-8033.

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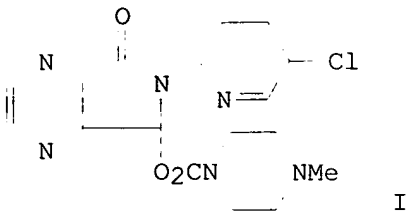

I

AB After acute administration of zopiclone (I) [43200-80-2] to mice and rats by different routes, the toxic symptoms appeared to be depression of spontaneous motor activity, depression of respiration, and a decrease in body wt. The LD50's were >3 1.2 mg/kg for all routes of administration; the LD50's were also similar in both males and females and in both mice and rats. Death occurred within 72 h for most of the animals. The cause of death appeared to be dyspnea following lethargy. Tonic convulsions were obsd. after i.v. administration in mice and rats and after i.m. administration in mice. Autopsy revealed no great changes except for discoloration of the liver and kidney in some of the animals.

TI Acute toxicity of **zopiclone** (27 267 **R**.P.) in mice and rats

L33 ANSWER 15 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 8

1984:191004 Document No.: BA77:23988. PLASMA CONCENTRATIONS AND CENTRAL NERVOUS SYSTEM EFFECTS OF THE NEW HYPNOTIC AGENT ZOPICLONE IN PATIENTS WITH CHRONIC LIVER DISEASE. PARKER G; ROBERTS C J C. CLINICAL PHARMACOL. UNIT, DEP. MED., BRISTOL ROYAL INFIRMARY, BRISTOL BS2 8HW.. BR J CLIN PHARMACOL, (1983) 16 (3), 259-266. CODEN: BCPHBM. ISSN: 0306-5251. Language: English.

AB Healthy individuals (8) and 7 cirrhotic patients received 7.5 mg zopiclone orally. Two further cirrhotics received 3.75 mg. Plasma concentrations of zopiclone and psychometric tests including reaction time and critical flicker fusion threshold and EEG tracings were performed at regular intervals after drug administration. Peak plasma levels of zopiclone were similar in the 2 groups but the time to peak was delayed in the cirrhotics. Plasma zopiclone half-life was 8.53 .+-. 0.83 h in the cirrhotics and 3.50 .+-. 0.33 h in the healthy individuals. In the group of cirrhotics, there was a negative correlation between **zopiclone** half-life and serum albumin concentration (**r** = -0.87). **Zopiclone** caused sedation in both groups. Reaction time was prolonged and critical flicked fusion threshold reduced in both groups. Recovery was delayed in the cirrhotics compared to the healthy subjects but was complete by 8 h. The size of the changes was somewhat greater in the cirrhotics but baseline observations differed between the groups. The

mean dominant frequency was lower in the cirrhotics and fell slightly in that group after zopiclone administration. The response to zopiclone is delayed and exaggerated in cirrhosis. Precautions are therefore required when using this drug in patients with chronic liver disease.

AB Healthy individuals (8) and 7 cirrhotic patients received 7.5 mg zopiclone orally. Two further cirrhotics received 3.75 mg. Plasma concentrations of zopiclone and psychometric tests including reaction time and critical flicker fusion threshold and EEG tracings were performed at regular intervals after drug administration. Peak plasma levels of zopiclone were similar in the 2 groups but the time to peak was delayed in the cirrhotics. Plasma zopiclone half-life was 8.53 .+-. 0.83 h in the cirrhotics and 3.50 .+-. 0.33 h in the healthy individuals. In the group of cirrhotics, there was a negative correlation between **zopiclone** half-life and serum albumin concentration (**r** = -0.87). **Zopiclone** caused sedation in both groups. Reaction time was prolonged and critical flicked fusion threshold reduced in both groups. Recovery was delayed in the cirrhotics compared to the healthy subjects but was complete by 8 h. The size of the changes was somewhat greater in the cirrhotics but baseline observations differed between the groups. The mean dominant frequency was lower in the cirrhotics and fell slightly in that group after zopiclone administration. The response to zopiclone is delayed and exaggerated in cirrhosis. Precautions are therefore required when using this drug in patients with chronic liver disease.

L33 ANSWER 16 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

84056590 EMBASE Document No.: 1984056590. Effectiveness of zopiclone as a preoperative hypnotic. Momose T.. Nagoya National Hospital, Nagoya, Japan. Pharmacology 27/SUPPL. 2 (196-204) 1983.
CODEN: PHMGBN. Pub. Country: Switzerland. Language: English.

AB A controlled, double-blind study was made of the efficacy and safety of a new hypnotic, **zopiclone**, on the preoperative night**'s** sleep by a Joint Study Unit Group of the anesthesiology departments in 6 national hospitals. The following results were found: (1) zopiclone 7.5 and 10 mg and nitrazepam 10 mg were significantly superior to placebo both in the quality of sleep and the mental state of the patient, while no significant differences were observed among these three active drugs; (2) a significantly higher incidence of side-effects was observed for nitrazepam 10 mg than for zopiclone 7.5 and 10 mg and placebo; (3) zopiclone 7.5 and 10 mg and also nitrazepam 10 mg were significantly more useful than placebo, and (4) the above results show that 7.5 and 10 mg of **zopiclone** are of great benefit to the preoperative night**'s** sleep and have less side-effects than 10 mg of nitrazepam.

AB A controlled, double-blind study was made of the efficacy and safety of a new hypnotic, **zopiclone**, on the preoperative night**'s** sleep by a Joint Study Unit Group of the anesthesiology departments in 6 national hospitals. The following results were found: (1) zopiclone 7.5 and 10 mg and nitrazepam 10 mg were significantly superior to placebo both in the quality of sleep and the mental state of the patient, while no significant differences were observed among these three active drugs; (2) a significantly higher incidence of side-effects was observed for nitrazepam 10 mg than for zopiclone 7.5 and 10 mg and placebo; (3) zopiclone 7.5 and 10 mg and also nitrazepam 10 mg were significantly more useful than placebo, and (4) the above results show that 7.5 and 10 mg of **zopiclone** are of great benefit to the preoperative night**'s** sleep and have less side-effects than 10 mg of nitrazepam.

L33 ANSWER 17 OF 19 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

80116321 EMBASE Document No.: 1980116321. [Study of vigilance after ingestion of zopiclone in comparison with nitrazepam and placebo: Methodology: Self-rating questionnaire and psychometric tests]. ETUDE DE LA VIGILANCE APRES PRISE DE **ZOPICLONE** EN COMPARAISON AVEC NITRAZEPAM ET PLACEBO. METHODOLOGIE DE **L'**ETUDE: QUESTIONNAIRES

Searched by: Mary Hale 308-4258 CM-1 12D16

D'AUTO-EVALUATION ET TESTS PSYCHOMETRIQUES. Lemperiere Th.; Sarrazin A.; Feline A.; et al.. Hop. Louis Mourier, F 92701 Colombes Cedex, France. Encephale 6/1 (23-35) 1980.
CODEN: ENCEAN. Pub. Country: France. Language: French. Summary Language: English.

AB Increasing importance is being given to the residual effects of hypnotics on the day following absorption; with zopiclone, a new hypnotic, we have studied vigilance 9, 12 and 15 hours after a single evening dose of 10 mg on a double-blind basis in comparison with 10 mg of nitrazepam and a placebo. The assessment of vigilance is based on responses to self-rating questionnaires and psychometric tests. Twenty-one healthy subjects forming a homogeneous group as regards age, I.Q., and vigilance were included in this study. Each subject received the 3 products in random distributed order, with an interval of 3 months between each trial. The results of these tests reveal modifications which, particularly 9 hours after administration, reflect a modification in vigilance, appearing to be more marked with nitrazepam than with zopiclone. Thus, from the point of view of the residual effects of hypnotics on vigilance, it is possible to position the products tested in the following order: placebo - zopiclone - nitrazepam.

TI [Study of vigilance after ingestion of zopiclone in comparison with nitrazepam and placebo: Methodology: Self-rating questionnaire and psychometric tests].
ETUDE DE LA VIGILANCE APRES PRISE DE **ZOPICLONE** EN COMPARAISON AVEC NITRAZEPAM ET PLACEBO. METHODOLOGIE DE **L**'ETUDE: QUESTIONNAIRES D'AUTO-EVALUATION ET TESTS PSYCHOMETRIQUES.

L33 ANSWER 18 OF 19 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1979:273138 Document No.: BA68:75642. IN-VITRO AND IN-VIVO INHIBITION BY **ZOPICLONE R**-27-267 OF BENZODIAZEPINE BINDING TO RODENT BRAIN RECEPTORS. BLANCHARD J C; GARRET C; JULOU L; BIOREAU A. RHONE-POULENC RES., CENT. NICOLAS GRILLET, F 94400 VITRY-SUR-SEINE, FR.. LIFE SCI, (1979) 24 (26), 2417-2420. CODEN: LIFSAK. ISSN: 0024-3205. Language: English.

AB Drugs which inhibit the binding of benzodiazepines to rat brain receptors are members of this chemical family. Zopiclone (RP 27 267), a new drug with a pharmacological profile similar to that of chlordiazepoxide and nitrazepam but chemically different from benzodiazepines, was tested for its ability to inhibit benzodiazepine binding. In vitro and in vivo studies showed that zopiclone inhibits the binding of [3H] diazepam and [3H] flunitrazepam to brain receptors. The potency of zopiclone is comparable to that of diazepam and nitrazepam in vitro and to that of chlordiazepoxide in vivo. Apparently there are pharmacological similarities between zopiclone and the benzodiazepines.

TI IN-VITRO AND IN-VIVO INHIBITION BY **ZOPICLONE R**-27-267 OF BENZODIAZEPINE BINDING TO RODENT BRAIN RECEPTORS.

L33 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2002 ACS
1979:137765 Document No. 90:137765 Synthesis of 6-(5-chloropyrid-2-yl)-5-(4-methylpiperazin-1-yl)carbonyloxy-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine. Jeanmart, Claude; Cotrel, Claude (Cent. Nicolas-Grillet, Rhone-Poulenc Rech., Vitry-sur-Seine, Fr.). C. R. Hebd. Seances Acad. Sci., Ser. C, 287(9), 377-8 (French) 1978. CODEN: CHDCAQ. ISSN: 0567-6541.

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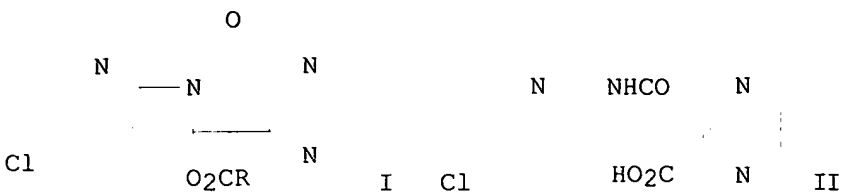

AB Title compd. I (**R** = 4-methyl-1-piperazinyl), **Zopiclone** , was prepd. by condensation of 2,3-pyrazinedicarboxylic anhydride with 2-amino-5-chloropyridine, cyclization of II in the presence of Ac2O, partial redn. of the resulting imide by KBH4, and esterification with RCOCl. I has anxiolytic and hypnotic activity (no data).

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L34 0 FILE MEDLINE
L35 10 FILE CAPLUS
L36 13 FILE BIOSIS
L37 15 FILE EMBASE
L38 0 FILE JICST-EPLUS

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L40 ANSWER 1 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
2001:563996 Document No.: PREV200100563996. Possible interaction of zopiclone and nefazodone. Alderman, Christopher P. (1); Gebauer, Markus G.; Gilbert, Andrew L.; Condon, John T.. (1) Quality Use of Medicine Pharmacy Research Center, University of South Australia, Daws Rd., Daw Park, South Australia, 5041: Chris.Alderman@rgh.sa.gov.au Australia. Annals of Pharmacotherapy, (November, 2001) Vol. 35, No. 11, pp. 1378-1380. print. ISSN: 1060-0280. Language: English. Summary Language: English; French; Spanish.

AB OBJECTIVE: To describe a case in which concurrent treatment with nefazodone was associated with an elevation in the plasma concentration of zopiclone, possibly resulting in enhanced hypnosedative efficacy. CASE REPORT: An 86-year old white woman was treated with nefazodone for depression. Zopiclone was also introduced for the management of insomnia, but she subsequently experienced morning drowsiness. The concentration of zopiclone in plasma was subsequently measured eight hours after administration on two occasions, during nefazodone therapy and after its withdrawal. After discontinuation of nefazodone, the plasma concentration of the **S**-enantiomer of **zopiclone** decreased from 107 to 16.9 ng/mL, while the **R**-enantiomer plasma concentration decreased from 20.6 to 1.45 ng/mL. DISCUSSION: Nefazodone is a relatively potent inhibitor of CYP3A4, a hepatic isoenzyme thought to play a major

role in the metabolic elimination of zopiclone. The substantial decrease in the plasma zopiclone concentrations observed after withdrawal of nefazodone likely reflects a drug interaction. Despite the normally short elimination half-life of zopiclone, the residual sedation initially observed in this case suggests that the interaction may have clinical significance. CONCLUSIONS: The features observed in this case suggest the possibility of a drug-drug interaction between nefazodone and zopiclone. Further prospective investigation is required to elucidate the nature and magnitude of this effect.

L40 ANSWER 2 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2001414139 EMBASE Fatal overdose of zopiclone in an elderly woman with bronchogenic carcinoma. Bramness J.G.; Arnestad M.; Karinen R.; Hilberg T.. Dr. J.G. Bramness, Natl. Inst. of Forensic Toxicology, P.O. Box 495 - Sentrum, N-0105 Oslo, Norway. Journal of Forensic Sciences 46/5 (1247-1249) 2001.
Refs: 14.
ISSN: 0022-1198. CODEN: JFSCAS. Pub. Country: United States. Language: English. Summary Language: English.
AB The death of a 72-year-old woman with respiratory debilitation due to bronchogenic carcinoma is described. She overdosed herself with probably 200 to 350 mg of zopiclone. Zopiclone, quantitated by HPLC in femoral postmortem blood, was found to be 1.9 mg/L (4.8 .mu.mol/**L**). This level is higher than many other **zopiclone** fatalities reported. We report a case where only zopiclone was detected.

L40 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2
2001:160739 Document No. 135:174433 **(S)-Zopiclone**
Sepracor. Georgiev, Vasil (Institute of Physiology, Bulgarian Academy of Sciences, Sofia, 113, Bulg.). Curr. Opin. Invest. Drugs (PharmaPress Ltd.), 2(2), 271-273 (English) 2001. CODEN: COIDAZ. Publisher: PharmaPress Ltd..
AB A review with 14 refs. **(S)-Zopiclone**, a cyclopyrrolone sharing activity with benzodiazepines in the CNS, is a short-acting sedative being developed by Sepracor for the potential treatment of sleeping disorders. In August 2000, the company had completed phase II trials of (S)- for insomnia; by Sept. 2000, patient enrollment for phase III studies for insomnia was completed and the trial initiation was planned for Oct. 2000. Merrill Lynch expects US filing to take place in the second half of 2001. Sepracor was granted US-05786357 in August 1998 covering methods and compns. of **(S)-zopiclone** in the treatment of sleeping disorders.

L40 ANSWER 4 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2002030142 EMBASE Use of prescription and nonprescription hypnotics in a Canadian elderly population. Busto U.E.; Sproule B.A.; Knight K.; Herrmann N.. Dr. U.E. Busto, Centre for Addiction/Mental Health, Addiction Research Foundation Site, 33 Russell Street, Toronto, Ont. M5S 2S1, Canada. usoa_busto@camh.net. Canadian Journal of Clinical Pharmacology 8/4 (213-221) 2001.
Refs: 25.
ISSN: 1198-581X. CODEN: CJCPFB. Pub. Country: Canada. Language: English. Summary Language: English; French.
AB Background: Hypnotics are commonly used by older adults, yet little is known about the patterns of their use and effectiveness in this population. Methods: Three thousand eight hundred sixty anonymous, self-report surveys were distributed to community pharmacies (n=356) across Canada to obtain information on the patterns of use of hypnotics from elderly volunteers. Results: The mean age of respondents was 72.+-.7 years (range 60 to 95 years) and 66% were women. In the past year, 53% of respondents used hypnotics. Prescription products accounted for 83% of the past year's use (66% benzodiazepines, 11% **zopiclone**,

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4% antidepressants, 2% opioids), and 17% of the products used were over-the-counter (5% herbal, 5% antihistamines, 3% analgesics). Use was regular (50% daily) and chronic (mean duration six years: range two weeks to 30 years). Hypnotics significantly (P<0.001) improved subjective sleep latency (mean 32 min compared with 93 min), number of nocturnal awakenings (mean two compared with four) and total hours of sleep (mean 7 h compared with 4 h). Effectiveness was highly rated: at the most recent use of the product, mean 7.6 (SD.+-.2.2) of 10; initially, 7.9 (SD.+-.2.3) with a significance of P=0.02. Most respondents (59%) reported side effects, mainly dry mouth (30%), memory problems (22%) and daytime sleepiness (22%), although 60% rated the side effects as mild. The mean number of other medications used was five (range zero to 17). Of the 54 subjects who used nonprescription sleep products, only half (52%) indicated that their physician was aware of this use. Conclusions: Prescription drugs were primarily used for sleep and were perceived to be effective even with long term use, despite mild side effects.

L40 ANSWER 5 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3

2001:195006 Document No.: PREV200100195006. Sedative and anxiolytic effects of **zopiclone's** enantiomers and metabolite. Carlson, Jeffrey N. (1); Haskew, Rene; Wacker, Jennifer; Maisonneuve, Isabelle M.; Glick, Stanley D.; Jerussi, Thomas P.. (1) Center for Neuropharmacology and Neuroscience, Albany Medical College, 47 New Scotland Avenue, Albany, NY, 12208: carlsoj@mail.amc.edu USA. European Journal of Pharmacology, (16 March, 2001) Vol. 415, No. 2-3, pp. 181-189. print. ISSN: 0014-2999. Language: English. Summary Language: English.

AB We evaluated racemic **zopiclone**, its (**S**)- and (**R**)-enantiomers and a metabolite, (**S**)-desmethylzopiclone, for their actions on locomotor activity, rotarod performance, the elevated plus maze and the Vogel conflict test of anxiety, and electroconvulsive shock-induced seizures duration. **Zopiclone** and its (**R**)- and (**S**)-enantiomers reduced locomotor activity, and **zopiclone** and its (**S**)-enantiomer disrupted rotarod performance at 10 mg/kg. (S)-desmethylzopiclone did not alter these measures at doses of less than 200 mg/kg. (S)-desmethylzopiclone altered plus maze performance at the lowest dose of all the zopiclone derivatives tested, caused a dose-related effect on the Vogel conflict test and caused a dose-related reduction of electroconvulsive shock-induced seizure durations. The data indicate that (S)-desmethylzopiclone can bring about an anxiolyic effect without a substantial degree of central nervous system depression, and suggest that the agent may be particularly useful clinically in the treatment of anxiety.

L40 ANSWER 6 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2001:366583 Document No.: PREV200100366583. **(S)-Zopiclone**: An isomerically pure non-benzodiazepine hypnotic without respiratory depression. Powchik, P. (1); Cohn, M.. (1) Sepracor Inc., Marlborough, MA USA. Sleep (Rochester), (April 15, 2001) Vol. 24, No. Abstract Supplement, pp. A170. print. Meeting Info.: 15th Annual Meeting of the Associated Professional Sleep Societies Chicago, Illinois, USA June 05-10, 2001 ISSN: 0161-8105. Language: English. Summary Language: English.

L40 ANSWER 7 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4

2001:281112 Document No.: PREV200100281112. Drug-induced taste disorders: Analysis of the French Pharmacovigilance Database and literature review. Original Title: Troubles du gout d'origine medicamenteuse: Analyse de la Banque Nationale de Pharmacovigilance et revue de la litterature.. Ratrema, M. (1); Guy, C.; Nelva, A.; Benedetti, C.; Beyens, M. N.; Grasset, L.; Ollagnier, M.. (1) Centre Regional de Pharmacovigilance et de Renseignements sur le Medicament, Hopital de Bellevue, 42055,

Searched by: Mary Hale 308-4258 CM-1 12D16

Saint-Etienne Cedex 2 France. Therapie (London), (Janvier Fevrier, 2001) Vol. 56, No. 1, pp. 41-50. print. ISSN: 0040-5957. Language: French. Summary Language: English; French.

AB Taste disorders, generally poorly studied, have various causes. From 1985 to 1997, 305 observations of taste disorders imputed to drugs were notified to Regional Pharmacovigilance Centres. Patients were on average 54.4 years old and 58 per cent were women. Quantitative as well as qualitative disorders have been observed. Drugs mainly found were: angiotensin converting enzyme inhibitors, terbinafine, **zopiclone**, **D**-penicillamine, imidazole derivatives, quinolones, macrolides, carbimazole and calcium channel blockers. The outcome was favourable for 60.3 per cent of patients. The possible efficacy of zinc is discussed. It is generally considered that taste disorders are not a serious side-effect, but they can reduce the quality of life and lead to poor compliance with treatment.

L40 ANSWER 8 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

2001151697 EMBASE Synthesis of enantiomerically pure desmethylzopiclone and determination of its absolute configuration. Hong Y.; Bakale R.P.; Fang Q.K.; Xiang T.; Han Z.; McConville F.X.; Senanayake C.H.; Wald S.A.. Y. Hong, Chem. Process Research/Development, Sepracor Inc., 111 Locke Drive, Marlborough, MA 01752, United States. yhong@sepracor.com. Tetrahedron Asymmetry 11/23 (4623-4627) 1 Dec 2000.
Refs: 16.
ISSN: 0957-4166. CODEN: TASYE3.
Publisher Ident.: S 0957-4166(00)00455-9. Pub. Country: United Kingdom.
Language: English. Summary Language: English.

AB Two synthetic methods have been established for the preparation of enantiomerically pure desmethylzopiclone, a metabolite of **zopiclone**. In Method A, (**S**)-desmethylzopiclone was prepared by demethylation of (**S**)-**zopiclone** with 1-chloroethyl chloroformate in high yield. Enantiomerically pure **zopiclone** (>99% ee) was obtained through a highly efficient resolution process in >36% overall yield. In Method B, racemic desmethylzopiclone was resolved with L-N-benzyloxycarbonyl phenylalanine (L-ZPA) followed by recrystallization in good yield. The absolute stereochemistry of the (+)-enantiomer was first determined to be the (S)-configuration by X-ray crystallography. .COPYRGT. 2001 Elsevier Science Ltd.

L40 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2002 ACS

2000:796770 First practical synthesis of optically pure desmethylzopiclone and determination of its absolute configuration.. Hong, Yaping; Bakale, Roger P.; Senanayake, Chris H.; Fang, Q. Kevin; Xiang, Tingjian; Han, Zhengxu; McConville, Fran A.; Wald, Stephen A. (Chemical Process Research and Development, Sepracor Inc, Marlborough, MA, 01752, USA). Abstr. Pap. - Am. Chem. Soc., 220th, ORGN-268 (English) 2000. CODEN: ACSRAL. ISSN: 0065-7727. Publisher: American Chemical Society.

AB Two practical synthetic methods have been established for the prepn. of optically pure desmethylzopiclone, a metabolite of zopiclone. In Method A, (**S**)-desmethyl-**zopiclone** was prepd. by demethylation of optically pure **zopiclone** with 1-chloroethyl chloroformate in high yield. Optically pure **zopiclone** was obtained through a highly efficient resoln. process with **D**-malic acid. In Method B, racemic deszopiclone was resolved by L-N-benzyloxycarboxyl alanine followed by recrystn. in good yield. The abs. stereochem. of zopiclone and desmethylzopiclone were first detd. by single X-ray crystallog.

L40 ANSWER 10 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2001:134217 Document No.: PREV200100134217. Anxiolytic effects of the non-benzodiazepine agent S-desmethylzopiclone on the elevated plus maze. Carlson, J. N. (1); Haskew, R. E.; Maisonneuve, I. M.; Glick, S. D.;

Searched by: Mary Hale 308-4258 CM-1 12D16

Jerussi, T. P.. (1) Albany Medical College, Albany, NY USA. Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-659.11. print. Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience. ISSN: 0190-5295. Language: English. Summary Language: English.

AB Zopiclone is a member of a class of non-benzodiazepine agents that has been shown to have affinity for benzodiazepine receptors. These agents, when compared to the benzodiazepines, have generally had weaker anxiolytic effects in animal models. For example, zopiclone displays anxiolytic activity in the plus-maze test in rats only at doses close to those producing motor impairment. Little is known, however, about the potential anxiolytic activity of (**S**)-desmethylzopiclone (DEZOP), a metabolite of **zopiclone**. We compared the effects of DEZOP to those of zopiclone and the benzodiazepine alprazolam on elevated plus-maze performance. Each drug was also assessed for effects on rotorod performance and spontaneous locomotor activity. All three drugs significantly increased the percent of time spent in open arms, indicating anxiolytic activity. Zopiclone increased this measure at 10mg/kg, a dose that also impaired rotorod performance. However, DEZOP increased open-arm time at 2.5 mg/kg but did not impair rotorod performance at doses less than 200 mg/kg. Alprazolam increased open-arm time at 1 mg/kg and impaired rotorod performance at 5 mg/kg. These findings indicate that an anxiolytic effect of DEZOP occurs at doses far below those producing motor impairment and suggest that it may be clinically useful in the treatment of anxiety.

L40 ANSWER 11 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

2000:19009 Document No.: PREV200000019009. Sleep in fibromyalgia patients: Subjective and objective findings. Harding, Susan M. (1). (1) UAB Sleep/Wake Disorders Center, University of Alabama at Birmingham, 215 Tinsley Harrison Tower, Birmingham, AL, 35294 USA. American Journal of the Medical Sciences, (June, 1998) Vol. 315, No. 6, pp. 367-376. ISSN: 0002-9629. Language: English. Summary Language: English.

AB Fibromyalgia (FM) patients report early morning awakenings, awakening feeling tired or unrefreshed, insomnia, as well as mood and cognitive disturbances; they may also experience primary sleep disorders including sleep apnea. Longitudinal studies have demonstrated the chronic nature of these disturbances in patients with FM. A distinct relationship exists between poor sleep quality and pain intensity. Polysomnographic findings during sleep in these patients include an alpha frequency rhythm, termed alpha-delta sleep anomaly, which is also seen in normal controls during stage 4 sleep deprivation; deep pain induced during sleep in normal controls also causes this anomaly. Sleep architecture is altered in FM patients showing an increase in stage 1, a reduction in delta sleep, and an increased number of arousals. Before prescribing pharmacologic compounds aimed at modifying sleep, adequate pain control and sleep habits should be achieved; tricyclic antidepressants, trazadone, **zopiclone**, an **d** selective serotonin reuptake inhibitors, however, may be required. More research is needed to elucidate the cellular and molecular mechanisms involved in the sleep disturbances occurring in patients with FM.

L40 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 5

1999:237775 Document No. 130:306507 Treatment of insomnia by concomitant therapy with **Zopiclone** and Aniracetam in patients with cerebral infarction, cerebroatrophy, Alzheimer's disease and Parkinson's disease. Katsunuma, H.; Shimizu, T.; Ogawa, K.; Kubo, H.; Ishida, H.; Yoshihama, A. (Department of Internal Medicine, Tachikawa Medical Center, Omotemachi Hospital, Nagoya, Japan). Psychiatry Clin. Neurosci., 52(2), 198-200 (English) 1998. CODEN: PCNEFP. ISSN: 1323-1316. Publisher: Blackwell Science Asia Pty Ltd..

AB For insomniac patients, sleeping drugs are used; in addn., concomitant therapy with other drugs has been tried in an effort to prevent a decrease

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in the effects due to long-term continuous use. This report presents the results of a study on the sleeping effects in nine aged patients with insomnia assocd. with cerebrovascular and non-cerebrovascular disorders who received concomitant therapy with Zopiclone and Aniracetam. The treatment in 7/9 cases (78%) was found to be effective, showing more than 50% prolongation of sleeping time, and in two cases (22%) was found to be ineffective. We discuss the mechanism of action referring to the literature.

L40 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 6
1998:790229 Document No. 130:191736 Residual effects of evening and middle-of-the-night administration of zaleplon 10 and 20 mg on memory and actual driving performance. Vermeeren, A.; Danjou, P. E.; O'Hanlon, J. F. (Experimental Psychopharmacology Unit (formerly Institute for Human Psychopharmacology), Maastricht University, Maastricht, Neth.). Hum. Psychopharmacol., 13(Suppl. 2), S98-S107 (English) 1998. CODEN: HUPSEC. ISSN: 0885-6222. Publisher: John Wiley & Sons Ltd..
AB This study was conducted to det. whether middle-of-the-night administration of the hypnotic zaleplon affects memory or driving performance the following morning. Healthy volunteers participated in a double-blind, 7-way, crossover study. They ingested capsules twice on each treatment night: once before initiating sleep and again after being briefly awakened 5 h later. Treatments were: placebo at both times, zaleplon at 10 or 20 mg, or zopiclone at 7.5 mg followed by placebo, or the same in reverse order. The subjects arose 3 h after the 2nd dose. One hour later, sleep quality and mood were assessed by questionnaires, and balance and memory in a test battery. A standardized actual driving test was undertaken 5-6 h after the 2nd dose. Both drugs similarly improved sleep quality, but only zopiclone hindered awakening. Evening zaleplon doses were without significant effects. Late-night zaleplon had minor effects in 1 memory test. Evening zopiclone shared these effects and also impaired driving performance. Late-night **zopiclone' s** effects were significant in every test. Its effects on driving were severe. The results suggest that 10 mg zaleplon certainly, and 20 mg probably, can be taken at bedtime or later in the night, .ltoreq.5 h before driving, with little risk of serious impairment.

L40 ANSWER 14 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
1998152955 EMBASE [Zopiclone and delirium: A case report [2]]. **ZOPICLONE** ET DELIRE: A PROPOS **D'**UNE OBSERVATION. David M.; Breton J.L.; Guy I.; Vandel S.. M. David, Centre de Pharmacovigilance, Pr. Bechtel, Chru J. Minjoz, 25030 Besancon Cedex, France. Therapie 53/1 (78-80) 1998.
Refs: 11.
ISSN: 0040-5957. CODEN: THERAP. Pub. Country: United Kingdom. Language: French.

L40 ANSWER 15 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
97158814 EMBASE Document No.: 1997158814. Concentrations and effects of zopiclone are greatly reduced by rifampicin. Villikka K.; Kivisto K.T.; Lamberg T.S.; Kantola T.; Neuvonen P.J.. Dr. K. Villikka, Department of Clinical Pharmacology, University of Helsinki, Haartmaninkatu 4, FIN-00290 Helsinki, Finland. British Journal of Clinical Pharmacology 43/5 (471-474) 1997.
Refs: 16.
ISSN: 0306-5251. CODEN: BCPHBM. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB Aims: The effects of rifampicin on the pharmacokinetics and pharmacodynamics of zopiclone, a non-benzodiazepine hypnotic, were studied. Methods: In a randomized, placebo-controlled cross-over study with two phases, eight young healthy volunteers took either 600 mg rifampicin or placebo once daily for 5 days. On the 6th day, 10 mg

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zopiclone was administered orally. Plasma zopiclone concentrations and effects of zopiclone were measured for 10 h. Results: The total area under the plasma zopiclone concentration-time curve after rifampicin was 18.0% (95% CI 13.5-22.5%) of that after placebo (86.1 .+-. 34.5 ng ml-1 h vs 473 .+-. 114 ng ml-1 h (mean.+-.s.d.); P<0.001). Rifampicin decreased the peak plasma concentration of **zopiclone** from 76.9 .+-. 27.2 ng ml-1 to 22.5 .+-. 6.0 ng ml-1 (P<0.001) and the half-life from 3.8 .+-. 0.6 h to 2.3 .+-. 0.9 h (P<0.005). A significant (P<0.02) reduction in the effects of zopiclone was seen in three of the five psychomotor tests used (digit symbol substitution test, critical flicker fusion test and Maddox wing test) after rifampicin pretreatment. Conclusions: The strong interaction of rifampicin with zopiclone is due to enhanced metabolism of zopiclone. Zopiclone may show a reduced hypnotic effect when used concomitantly with rifampicin or other potent inducers of CYP3A4 such as phenytoin and carbamazepine.

L40 ANSWER 16 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7

1999:113809 Document No.: PREV199900113809. Zopiclone fatality in a hospitalized patient. Meatherall, Robert C. (1). (1) Dep. Biochem., St. Boniface Gen. Hosp., 409 Tache Ave., Winnipeg, MB R2H 2A6 Canada. Journal of Forensic Sciences, (March, 1997) Vol. 42, No. 2, pp. 340-343. ISSN: 0022-1198. Language: English.

AB The death of a 72-year-old man is described who overdosed himself while in hospital. The man was being treated for lung cancer and ingested 90 mg of zopiclone in a suicide attempt. He died between 4 and 10 h after the ingestion. Zopiclone, quantitated by GC-MS in the femoral blood, cardiac blood, vitreous humor, urine and bile was found to be 254, 408, 94, 7,330, and 114,700 ng/mL, respectively. Considering the man's weakened physical condition, 90 mg could represent a minimum lethal **zopiclone** dose.

L40 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2002 ACS

1997:629863 Document No. 127:288058 Multidrug comparison (Lorazepam, Triazolam, Zolpidem, and Zopiclone) in situational insomnia: polysomnographic analysis by means of the cyclic alternating pattern. Parrino, Liborio; Boselli, Mirella; Spaggiari, Maria Cristina; Smerieri, Arianna; Terzano, Giovanni (Sleep Disorders Center, Inst. Neurology, Univ. Parma, Parma, Italy). Clin. Neuropharmacol., 20(3), 253-263 (English) 1997. CODEN: CLNEDB. ISSN: 0362-5664. Publisher: Lippincott-Raven.

AB Since homogeneous samples of insomniacs are difficult to recruit for pharmacotherapy studies, normal; sleepers can be used to assess the protective effect of hypnotic drugs, under standardized nonconductive conditions. In particular, a noisy environment is a typical cause of situational insomnia that can be counteracted by a sedative-hypnotic agent. Six healthy middle-aged subjects (three men and three women), with no complaints about sleep, underwent a completely randomized double-blind series of 10 nocturnal polysomnograms with at least 72-h washout intervals. All subjects received s single dose of placebo, zolpidem 10 mg, **zopiclone** 7.5 mg, lorazepam 1 mg, and triazolam 0.25 mg both under basal and under perturbed conditions. For each individual, five recordings were carried out under basal conditions (sound pressure level not higher than 30 dB) and five recordings under acoustically perturbed conditions (continuous white noise at 55 dB). Sleep quality was assessed by a visual analog scale (VAS). All recordings were scored according to conventional rules (macro-structure) and cyclic alternating pattern (CAP) methodol. (microstructure). Statistical anal. was based on a repeated measures anal.-of-variance design integrated by Bonferroni adjusted probabilities. Under placebo, situational insomnia was confirmed by the significant increase in sleep fragmentation (intrasleep wakefulness) and by the significant enhancement of arousal instability (CAP parameters). In contrast to macrostructural information,

CAP parameters were highly sensitive in detecting the perturbing effects of noise (mean CAP rate under placebo, 57%) and the protective action of hypnotic drugs during perturbation (mean CAP rate under active medication, 41%). Microstructural anal. enabled us to discriminate hypnotic drugs from placebo, nonbenzodiazepine compds. from benzodiazepine agents, and zopiclone from zolpidem. The latter, in fact, induced the lowest values of CAP rate both under basal (30%) and under noisy (39%) conditions and detd. a significant decrease in EEG arousals. All CAP parameters were significantly correlated with the visual-analog-scale scores for sleep quality. The use of CAP methodol. in a highly standardized model of situational insomnia can be a valid alternative to conventional sleep scoring for the investigation of drug effects on disturbed sleep.

L40 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2002 ACS
1997:348230 Document No. 127:46138 Detection of 2-amino-5-chloropyridine in urine as a parameter of zopiclone (Imovane) intake using HPLC with diode array detection. Mannaert, Erik; Tytgat, Jan; Daenens, Paul (Lab. of Toxicol., Katholieke Univ. Leuven, Louvain, B-3000, Belg.). J. Anal. Toxicol., 21(3), 208-212 (English) 1997. CODEN: JATOD3. ISSN: 0146-4760. Publisher: Preston Publications.
AB A qual. screening technique was developed for the detection of 2-amino-5-chloropyridine, an newly identified decompn. product of zopiclone and metabolites after alk. hydrolysis of urine samples. The method was elaborated using a std. operation procedure (Merck Tox Screening System), combining a solid-phase extn. with reversed-phase high-performance liq. chromatog. and diode array detection. **1** The limit of detection, expressed as **zopiclone** concns. in spiked urine, was 0.5 .mu.g/mL. Field urine samples from a volunteer were pos. for 2-amino-5-chloropyridine until 16 h after ingestion of one therapeutic dose of Imovane (7.5 mg zopiclone).

L40 ANSWER 19 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 8
1996:128926 Document No.: PREV199698701061. Enantioselective determination of zopiclone and its metabolites in urine by capillary electrophoresis. Hempel, G.; Blaschke, G. (1). (1) Inst. Pharm. Chem., Univ. Muenster, Hittorstr. 58-62, D-48149 Muenster Germany. Journal of Chromatography B Biomedical Applications, (1996) Vol. 675, No. 1, pp. 139-146. ISSN: 0378-4347. Language: English.
AB A method has been developed for the stereoselective determination of zopiclone and its main metabolites in urine. After the addition of the internal standard zolpidem the urine samples were extracted at pH 8 with chloroform-isopropanol (9:1). Analyses were carried out using capillary electrophoresis (CE) with beta-cyclodextrin as the chiral selector. The analytes were detected using UV laser-induced fluorescence detection with a He-Cd laser operated at 325 nm. Urine samples of two volunteers after oral administration of 7.5 mg **zopiclone** were investigated. The **S**-(+)-enantiomers of **zopiclone** and its metabolites were always excreted in higher amounts than the **R**-(-)-enantiomers. With the same method the **zopiclone** enantiomers were quantified in saliva. Compared to high-performance liquid chromatography, the CE method is very fast and simple.

L40 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 9
1996:162418 Document No. 124:223501 Two cases of fatal zopiclone overdose. Boniface, Peter J.; Russell, Sarah G. G. (Institute Environmental Science Research Limited, Auckland, N. Z.). J. Anal. Toxicol., 20(2), 131-3 (English) 1996. CODEN: JATOD3. ISSN: 0146-4760.
AB Two cases of death due to the ingestion of zopiclone are presented. Quant. detns. of **zopiclone** yielded 1.4-3.9 mg/**L** in the blood, 0.81 and 8.7 mg/kg in the liver, and 13.5 and 133 mg in the stomach contents. Drug concns. were interpreted relative to the case findings,

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published data, and a limited evaluation of therapeutic concns. found in two cases of therapeutic zopiclone use. Zopiclone was extd. from buffered blood or digested liver or both with Bu chloride and analyzed by high-performance liq. chromatog. with UV detection. Liver samples were digested at pH 7 to avoid zopiclone decompn.

L40 ANSWER 21 OF 25 CAPLUS COPYRIGHT 2002 ACS
1996:482622 Document No. 125:167917 Synthesis of a new chemical class of sedative-hypnotic zopiclone analogs. Zuo, Daishu; Zhang, Yafang; Shen, Jianmin; Li, Yijie (Dep. Organic Chem., Shenyang Pharmaceutical univ., Shenyang, 110015, Peop. Rep. China). Zhongguo Yaowu Huaxue Zazhi, 6(1), 26-30 (Chinese) 1996. CODEN: ZYHZEF.

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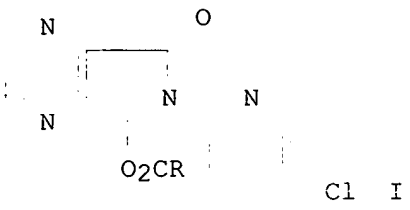

AB **Zopiclone** analogs I (**R** = 3-MeC6H4O, Ph, substituted Ph, 4-benzylpiperazino, PhCH:CH) were prepd. in 4 steps starting from 2,3-pyrazinedicarboxylic anhydride and 2-amino-5-chloropyrimidine. I showed sedative-hypnotic activity inferior to that of zopiclone.

L40 ANSWER 22 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1995:491522 Document No.: PREV199598505822. Zopiclone abuse in South Wales: The case reports. Sullivan, Gary (1); McBride, Andrew J.; Clee, William B.. (1) Llwyn-yr-Eos Clin., Main Rd., Church Village, Pontypridd, Mid-Glamorgan CF38 1RN UK. Human Psychopharmacology, (1995) Vol. 10, No. 4, pp. 351-352. ISSN: 0885-6222. Language: English.
AB Three cases of zopiclone abuse in South Wales are described. Two involve oral use with alcohol, and one of intravenous use. It appears that **zopiclone** has become widely available 'on the street' in parts of **S.** Wales where they are called 'zim-zims'. The implications are discussed.

L40 ANSWER 23 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 10
1996:81977 Document No.: PREV199698654112. **Zopiclone's** residual effects on psychomotor and information processing skills involved in complex tasks such as car driving: A critical review. O'Hanlon, J. F.. Inst. Human Psychopharmacol., Univ. Limburg, Abstraat 2A, 6211 LS, Maastricht Netherlands. European Psychiatry, (1995) Vol. 10, No. SUPPL. 3, pp. 137S-143S. ISSN: 0924-9338. Language: English.
AB Before and after its introduction in 1987, zopiclone was the object of investigation in 16 psychometric studies employing both healthy volunteers and insomniac patients. Their common purpose was to determine whether nocturnal doses (usually the standard 7.5 mg) possess residual sedative effects that interfere with skilled safety-relevant performance, such as car driving, over the following day. Most studies have found no residual effects. Those that did, have shown them to be modest in magnitude and not to persist for longer than about 12 hours from the time of dosage. Without altering the general conclusion that zopiclone possesses few if any residual effects of clinical relevance, it must be said that the studies reviewed failed to meet current methodological standards and may have left some important questions unanswered.

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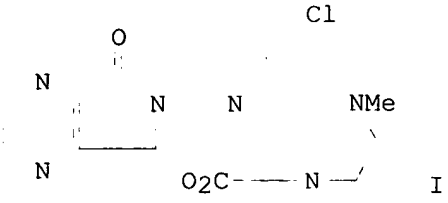
L40 ANSWER 24 OF 25 CAPLUS COPYRIGHT 2002 ACS
1993:480394 Document No. 119:80394 Electrochemical behavior of zopiclone. Vire, J. C.; Zhang, H.; Quarin, G.; Patriarche, G. J.; Senturk, Z.; Christian, G. D. (Inst. Pharm., Free Univ. Brussels, Brussels, B-1050, Belg.). Talanta, 40(3), 313-23 (English) 1993. CODEN: TLNTA2. ISSN: 0039-9140.

GI



I

AB The electrochem. properties of zopiclone(I), an anxiolytic and hypnotic drug, were investigated by different techniques. The compd. was reduced in two 2-electron steps in the pH range 0-12. The first step, which corresponds to the redn. of the pyrazine ring, is reversible in acidic and neutral solns. Strong adsorption phenomena accompany the redn. process in acidic and neutral media. **Zopiclone** was quant. measured over the entire pH range using **d**.c. polarog. However, the use of differential pulse and square-wave modes for quant. measurements is more limited due to a slope modification in the current-concn. relationship. Adsorptive stripping voltammetry can be applied to the detn. of low levels of the drug at pH 9, but only short deposition times may be used because large amts. of material accumulated under stirring conditions due to fast adsorption kinetics are rapidly released from the electrode surface. Detection limits are 1 .times. 10-7M and 2 .times. 10-10M for polarog. and adsorptive stripping voltammetry, resp. Only the first wave is of anal. interest for both techniques.

L40 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 11
1992:34402 Document No. 116:34402 Effects of buspirone and other anxiolytics on punished key-pecking in the pigeon. Nanry, Kevin P.; Howard, James L.; Pollard, Gerald T. (Pharmacol. Div., Burroughs Wellcome Co., Research Triangle Park, NC, 27709, USA). Drug Dev. Res., 24(3), 269-76 (English) 1991. CODEN: DDREDK. ISSN: 0272-4391.

AB Pigeons were trained to peck a key on a multiple schedule of reinforcement in which 30 responses in the presence of a white cue light produced 3 s of access to food, and 30 responses in the presence of a red cue light produced 3 s of access to food and an elec. shock, which suppressed responding. I.m. injection of the sedative-hypnotic anxiolytics chlordiazepoxide (0.3-10 mg/kg), alprazolam (0.1-3.0 mg/kg), and zopiclone (10-100 mg/kg) substantially increased punished responding. The nonsedative anxiolytics buspirone (0.1-3.0 mg/kg) and ipsapirone (1.0 and 3.0 mg/kg) increased punished responding as much as did the sedative-hypnotics. Buspirone had similar effects in benzodiazepine-naive and benzodiazepine-experienced pigeons. Chlorpromazine (tested at 1-30 mg/kg) and imipramine (tested at 1-30 mg/kg) only decreased unpunished responding at high doses. These results show that (1) the antipunishment effects of buspirone and ipsapirone in the pigeon are replicable in another lab., (2) buspirone**'s** effect occurs in benzodiazepine-experienced pigeons, and (3) alprazolam and **zopiclone** have antipunishment effects in the pigeon.

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L1 1 138729-47-2/RN

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L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **138729-47-2** REGISTRY
CN 1-Piperazinecarboxylic acid, 4-methyl-, (5S)-6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester, (S)-
CN 5H-Pyrrolo[3,4-b]pyrazine, 1-piperazinecarboxylic acid deriv.
OTHER NAMES:
CN (+)-Zopiclone
FS STEREOSEARCH
MF C17 H17 Cl N6 O3
CI COM
SR CA
LC STN Files: BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CEN, CIN, DRUGNL, DRUGPAT, DRUGUPDATES, PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL

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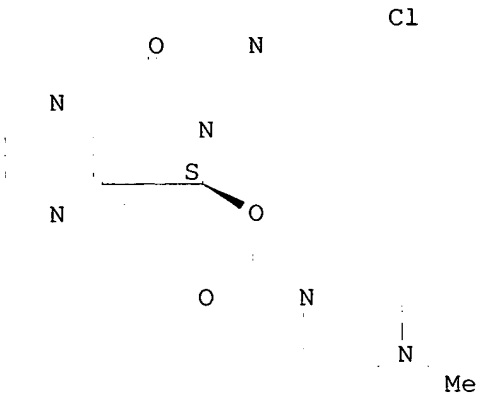
Absolute stereochemistry. Rotation (+).



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25 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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REFERENCE 5: 132:6266

REFERENCE 6: 131:277050

REFERENCE 7: 130:261430

REFERENCE 8: 129:221244

REFERENCE 9: 129:140784

REFERENCE 10: 128:167442

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L2 25 L1

L2 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2002 ACS
1997:808131 Document No. 128:106484 Separation of enantiomers of drugs by capillary electrophoresis V. Hydroxypropyl-.alpha.-cyclodextrin as chiral solvating agent. Koppenhoefer, Bernhard; Epperlein, Ulrich; Schlunk, Rainer; Zhu, Xiaofeng; Lin, Bingcheng (Auf der Morgenstelle 18, Institute for Organic Chemistry, University of Tubingen, D-72076 Tubingen, Germany). J. Chromatogr., A, 793(1), 153-164 (English) 1998. CODEN: JCRAEY. ISSN: 0021-9673. Publisher: Elsevier Science B.V..
AB In an extended chiral drug screening program, enantiosepn. of 86 racemic drugs was tested with hydroxypropyl-.alpha.-cyclodextrin as chiral solvating agent (CSA). A total of 34 drugs out of 86 could be resolved in this straightforward approach. The no. of expts. performed under identical conditions allows a correlation of the sepn. factors .alpha.m with the interaction strengths Rm. As shown for a subset of 23 drugs, the concn. of the CSA is a crucial parameter for further optimization.

L2 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2002 ACS
1997:283156 Document No. 127:17641 Enzymic resolution of (.+-.)-6-(5-chloropyridin-2-yl)-7-vinyloxycarbonyloxy-6,7-dihydro[5H]pyrrolo[3,4-b]pyrazin-5-one. Synthesis of (+)-zopiclone. Gotor, Vicente; Limeres, Fernando; Garcia, Roberto; Bayod, Miguel; Brieva, Rosario (Departmento de Quimica Organica e Inorganica, Facultad de Quimica, Universidad de Oviedo, Oviedo, 33071, Spain). Tetrahedron: Asymmetry, 8(7), 995-997 (English) 1997. CODEN: TASYE3. ISSN: 0957-4166. OTHER SOURCES: CASREACT 127:17641. Publisher: Elsevier.
GI

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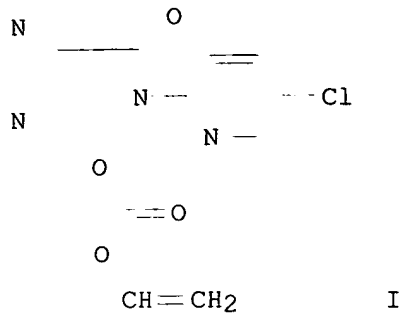

I

AB The lipase from Candida antarctica (CAL) catalyzes the resoln. of a precursor of zopiclone, I, through hydrolysis and transcarbonatation processes. I is then reacted with N-methylpiperazine to give (+)-zopiclone.

L2 ANSWER 13 OF 25 CAPLUS COPYRIGHT 2002 ACS
1996:668647 Document No. 125:339189 Capillary electrophoresis for separation of drug enantiomers using different cyclodextrins as chiral selectors. Ji, Yibing; Chen, Yuying; Lin, Bingchen (Department Analytical Chemistry, China Pharmaceutical University, Nanjing, 210038, Peop. Rep. China). Zhongguo Yaoke Daxue Xuebao, 27(6), 363-365 (Chinese) 1996. CODEN: ZHYXE9. ISSN: 1000-5048.

AB Ten compds. were chirally sepd. by adding .alpha.-, .beta.-, .gamma.-cyclodextrin (CD) as chiral selector, resp. Due to the different cavity sizes, .alpha.-, .beta.-,, .gamma.-CD had different selectivities to the compds. with different sizes and shapes, and the "size-match" principle and complexation between CD and the guest compds. was introduced to explain the exptl. results. The chiral recognition mechanism was further proved.

L2 ANSWER 14 OF 25 CAPLUS COPYRIGHT 2002 ACS
1996:580709 Document No. 125:264839 Development of a stereospecific radioimmunoassay for the analysis of zopiclone and metabolites in urine. Mannaert, Erik; Tytgat, Jan; Daenens, Paul (Lab. Toxicol., Kathol. Univ. Leuven, Louvain, B-3000, Belg.). Clin. Chim. Acta, 253(1,2), 103-115 (English) 1996. CODEN: CCATAR. ISSN: 0009-8981.

AB A sensitive and specific RIA has been developed, allowing the stereospecific detection of nanogram amts. of (+)- and (-)-enantiomers of zopiclone and its major metabolites in urine, without prior extn. or purifn. Antisera were obtained from two series of four rabbits, immunized with optically pure (+)- and (-)-N-hemisuccinyldesmethylzopiclone, conjugated to bovine serum albumin according to the active ester method. The assay was stereospecific, allowing discrimination between the two enantiomers of N-desmethylzopiclone with mutual cross-reactivities below 2%. Substantial cross-reaction was obsd. with the parent compd., although lower than expected, and to a lesser extent with the N-oxide metabolite. A selection of hypnotics, anxiolytics, antidepressants and some other widely used drugs did not interfere with the assay (<0 1%), when tested at a concn. level of 10 .mu./mL. The sensitivity of the assay was 50 pg/mL and 10 pg/mL for the (+)- and (-)-enantiomers, resp. The binding assay described here was used to evaluate the stereoselective excretion pattern of zopiclone. Anal. of cumulative excretion samples from a volunteer revealed a mean metabolic excretion ratio (+)/(-) of 2.2, ranging from 1.7 (7 h) to 4.4 (36 h). A mean excretion ratio of (+)/(-) of 2.5.+-.1 was calcd. for anal. of urine samples from 20 patients receiving zopiclone as a hypnotic daily.

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L2 ANSWER 15 OF 25 CAPLUS COPYRIGHT 2002 ACS
1996:460115 Document No. 125:184730 Semi-preparative chiral resolution of zopiclone and N-desmethylzopiclone. Mannaert, Erik; Daenens, Paul (Lab. Toxicol., Katholieke Univ. Leuven, Louvain, B-3000, Belg.). J. Pharm. Biomed. Anal., 14(8-10), 1367-1370 (English) 1996. CODEN: JPBADA. ISSN: 0731-7085.
AB Sepn. of the enantiomers was accomplished by liq. chromatog. using a com. available Chiralpak AS column. The asym. peak shape of (-)-N-desmethylzopiclone in comparison with that of (-)-zopiclone shows that the interaction of stereoisomers with the chiral stationary phase is crit. and often not predictable. Nonetheless, a max. load of 3 mg per injection could be achieved for the N-desmethyl metabolite. In one working week, about 100 mg of the enantiomers of N-desmethylzopiclone and about 50 mg of the enantiomers of zopiclone were collected in a pure state.

L2 ANSWER 16 OF 25 CAPLUS COPYRIGHT 2002 ACS
1996:348014 Document No. 125:96309 Separation of enantiomers of drugs by capillary electrophoresis. III. .beta.-cyclodextrin as chiral solvating agent. Koppenhoefer, B.; Epperlein, U.; Christian, B.; Lin, B.; Ji, Y.; Chen, Y. (University of Tuebingen, Auf der Morgenstelle 18, Tubingen, D-72076, Germany). J. Chromatogr., A, 735(1 + 2), 333-343 (English) 1996. CODEN: JCRAEY. ISSN: 0021-9673.
AB Enantiomer sepn. by capillary zone electrophoresis was studied for a set of 34 chiral drugs. Keeping the concn. of .beta.-cyclodextrin as a chiral solvating agent as const. as possible led to the sepn. of 7 enantiomeric pairs. Carvedilol, tetryzoline, tropicamide and zopiclone gave a baseline sepn., chlorphenamine, ketamine, and orciprenaline a partial sepn. Statistical anal. revealed that the best sepn. factors were obsd. for a medium degree of interaction with the cyclodextrin. A theory explaining this effect provides a helpful guideline for further optimization.

L2 ANSWER 17 OF 25 CAPLUS COPYRIGHT 2002 ACS
1996:77010 Document No. 124:193152 Enantioselective determination of zopiclone and its metabolites in urine by capillary electrophoresis. Hempel, G.; Blaschke, G. (Munster, D-48149, Germany). J. Chromatogr., B: Biomed. Appl., 675(1), 139-46 (English) 1996. CODEN: JCBBEP. ISSN: 0378-4347.
AB A method has been developed for the stereoselective detn. of zopiclone and its main metabolites in urine. After the addn. of the internal std. zolpidem the urine samples were extd. at pH 8 with chloroform-isopropanol (9:1). Analyses were carried out using capillary electrophoresis (CE) with .beta.-cyclodextrin as the chiral selector. The analytes were detected using UV laser-induced fluorescence detection with a He-Cd laser operated at 325 nm. Urine samples of two volunteers after oral administration of 7.5 mg zopiclone were investigated. The S-(+)-enantiomers of zopiclone and its metabolites were always excreted in higher amts. than the R-(-)-enantiomers. With the same method the zopiclone enantiomers were quantified in saliva. Compared to high-performance liq. chromatog., the CE method is very fast and simple.

L2 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2002 ACS
1995:713029 Document No. 123:132685 Degradation and racemization of zopiclone enantiomers in plasma and partially aqueous solutions. Fernandez, Christina; Gimenez, Francois; Mayrargue, Joelle; Thuillier, Alain; Farinotti, Robert (Service Pharmacie, Hopital Pitie-Salpetriere, Paris, Fr.). Chirality, 7(4), 267-71 (English) 1995. CODEN: CHRLEP. ISSN: 0899-0042.
AB We investigated the degrdn. and racemization zopiclone (ZOP) enantiomers in plasma and partially aq. solns. (ethanol:phosphate buffer). Degrdn. and racemization increased with increasing pH and temp. Degrdn. products were identified by means of mass spectrometry, which revealed hydrolysis

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of the carbamate function and opening of the pyrrolidone ring. In plasma, neither degrdn. nor racemization occurred after 6 mo of storage at -20.degree.C and subsequent extn.

L2 ANSWER 19 OF 25 CAPLUS COPYRIGHT 2002 ACS

1995:713028 Document No. 123:123299 Solvent selectivity in chiral chromatography using a .beta.-cyclodextrin-bonded phase. Piperaki, Stavroula; Tsantili-Kakoulidou, Anna; Parissi-Poulou, Maria (Dep. Pharmacy, Univ. Athens, Athens, Greece). Chirality, 7(4), 257-66 (English) 1995. CODEN: CHRLEP. ISSN: 0899-0042.

AB A .beta.-cyclodextrin-bonded phase has been used to investigate the sepn. of the enantiomers of atenolol, oxprenolol, celiprolol, tertatolol, terbutaline, fluoxetine, norfluoxetine, and zopiclone, focusing on the importance of solvent selectivity. With cyclodextrin (CD)-bonded phases, chiral discrimination occurs because the two enantiomers of a racemate form inclusion complexes of different strengths within the CD cavity. The org. modifier mols. tend to compete with solutes for a definite no. of adsorption sites on the stationary phase. Moreover, the ternary complex formation may play an important role in chiral recognition. In this study, it was of interest to est. the influence of mobile phase modifiers with respect to solvent type (i.e., MeCN, MeOH, EtOH, THF, i-PrOH, PrOH and t-BuOH), size and shape, and concns. Solvent selectivity has been investigated by using different org. modifiers in mobile phases with the same polarity, and relationships were established between the logarithm of solvent partition coeff. (log P2) and the three most important chromatog. parameters: retention time (t), resoln. (R), and enantioselectivity (.alpha.). Thus, it seems that they hydrophobicity of the org. modifier becomes one of the dominant factors affecting the inclusion process phenomena. Further, the apparent partition coeffs. of the compds. under study have been detd. and a comparison has been attempted regarding the degree of their enantiomeric resoln.

L2 ANSWER 20 OF 25 CAPLUS COPYRIGHT 2002 ACS

1994:594792 Document No. 121:194792 Stereospecific high-performance liquid chromatographic assay of zopiclone in human plasma. Foster, Robert T.; Caille, Gilles; Ngoc, Anh Ho; Lemko, Cathy H.; Kherani, Raheem; Pasutto, Franco M. (Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, T6G 2N8, Can.). J. Chromatogr., B: Biomed. Appl., 658(1), 161-6 (English) 1994. CODEN: JCBBEP.

AB A high-performance liq. chromatog. (HPLC) assay for the anal. of the enantiomers of zopiclone (ZPC), a cyclopyrrolone hypnotic, in plasma was developed. Following the addn. of chlordiazepoxide as internal std. (I.S.), plasma contg. the ZPC enantiomers and I.S. was extd. by liq.-liq. extn. at an alk. pH. After evapn. of the org. layer, the drug and I.S. were reconstituted in ethanol-hexane (80:20, vol./vol.) and injected onto the HPLC column. The enantiomers were sepd. at ambient temp. on a 25-cm Chiralcel OD-H column with ethanol-hexane (60:40, vol./vol.) as the mobile phase pumped at a flow-rate of 0.6 mL/min. The enantiomers of ZPC were quantified by fluorescence detection with excitation and emission wavelengths of 300 and 470 nm, resp. The assay described allows for the direct quantitation of ZPC without pre-column derivatization, and is suitable for clin. studies of ZPC in humans after administration of therapeutic doses.

L2 ANSWER 21 OF 25 CAPLUS COPYRIGHT 2002 ACS

1994:235291 Document No. 120:235291 Pharmacokinetics of zopiclone and its enantiomers in Caucasian young healthy volunteers. Fernandez, C.; Maradeix, V.; Gemenez, F.; Thuillier, A.; Farinotti, R. (Serv. Pharm. Pharmacocinet., Hop. Pitie Salpetriere, Paris, 75651, Fr.). Drug Metab. Dispos., 21(6), 1125-8 (English) 1993. CODEN: DMDSAI. ISSN: 0090-9556.

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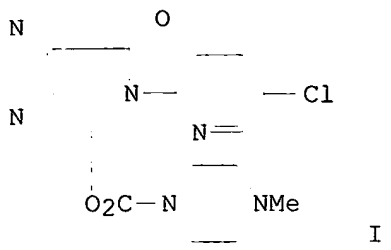

I

AB The disposition of the enantiomers of zopiclone (I) and its two chiral metabolites was investigated after oral administration of a single dose of 15 mg of a racemic mixt. (twice the usual therapeutic regimen) in 12 adult Caucasian volunteers. Detn. of concns. of zopiclone enantiomers in plasma showed that zopiclone pharmacokinetics is stereoselective with AUC0-.infin. values of 691.3 and 209.5 ng.mL-1.h ($p < 0.001$), Cmax value of 87.3 and 44.0 ng.mL-1 ($p < 0.001$), oral CLtot/F values of 195.5 and 659.8 mL.min-1 ($p < 0.001$), Vd/F values of 98.6 and 192.8 L ($p < 0.01$) and elimination half-life of 399.2 and 225.6 min ($p < 0.01$) for (+)-zopiclone and (-)-zopiclone, resp. On the contrary, absorption half-life and Tmax values were not significantly different. In 48-h urine, 3.6% of unchanged zopiclone was excreted, whereas 14.2% and 13.8% of both metabolites, N-desmethylzopiclone and N-oxideopiclone, resp., were found. Quantities of (+)-zopiclone excreted in urine were always higher compared with its antipode (-)-zopiclone for the 12 volunteers ($p < 0.001$). For the metabolites, quantities of both enantiomers were either equal or different and when different, it was always in favor of the (+)-enantiomer.

L2 ANSWER 22 OF 25 CAPLUS COPYRIGHT 2002 ACS

1994:22978 Document No. 120:22978 Determination of the enantiomers of zopiclone and its two chiral metabolites in urine using an automated coupled achiral-chiral chromatographic system. Fernandez, Christine; Gimenez, Francois; Baune, Bruno; Maradeix, Valerie; Thuillier, Alain (Serv. Pharm., Hop. Pitie Salpetriere, Paris, 75013, Fr.). J. Chromatogr., Biomed. Appl., 617(2), 271-8 (English) 1993. CODEN: JCBADL. ISSN: 0378-4347.

AB The enantiomers of zopiclone and its two chiral N-desmethyl and N-oxide metabolites were detd. in urine using a coupled achiral-chiral liq. chromatog. method. After liq.-liq. extn., zopiclone and its two metabolites were quantified on a cyanopropyl column. After fluorimetric detection on the achiral system, the eluent was switched through a silica precolumn in order to trap and conc. the analytes. Each fraction was then backflushed sep. onto a carbamate cellulose chiral stationary phase in order to det. the enantiomeric ratios. The coupled system was automated with an autosampler and a switching value programmed by an integrator. The method was validated, and a first trial was performed on urine samples of a volunteer treated with 15 mg of racemic zopiclone.

L2 ANSWER 23 OF 25 CAPLUS COPYRIGHT 2002 ACS

1993:463059 Document No. 119:63059 Treating sleep disorders, convulsive seizures, and other disorders using optically pure (+)-zopiclone. Young, James W.; Brandt, Steven (Sepracor, Inc., USA). PCT Int. Appl. WO 9310787 A1 19930610, 41 pp. DESIGNATED STATES: W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, UA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US10631 19921201. PRIORITY: US 1991-801312 19911202.

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AB (+)-Zopiclone (I) is effective in treating sleep disorders and convulsive disorders. I is free of the side effects of (.+-.)-zopiclone. I is also useful for treating disorders affected by the agonist binding to central nervous system or peripheral benzodiazepine receptors.

L2 ANSWER 24 OF 25 CAPLUS COPYRIGHT 2002 ACS
1992:591870 Document No. 117:191870 Preparation of (-)-zopiclone. Cotrel, Claude; Roussel, Gerard (Rhone-Poulenc Rorer S. A., Fr.). Eur. Pat. Appl. EP 495717 A1 19920722, 5 pp. DESIGNATED STATES: R: PT. (French). CODEN: EPXXDW. APPLICATION: EP 1992-400111 19920116. PRIORITY: FR 1991-490 19910117.
AB The title compd., prepd. by optical resoln. of racemic zopiclone as the D-(+)-O,O'-dibenzolyltartrate salt, is about twice as active as the racemate and had LD50 of .apprx.1.5 g/kg orally in mice.

L2 ANSWER 25 OF 25 CAPLUS COPYRIGHT 2002 ACS
1992:75574 Document No. 116:75574 Determination of zopiclone enantiomers in plasma by liquid chromatography using a chiral cellulose carbamate column. Fernandez, Christine; Baune, Bruno; Gimenez, Francois; Thuillier, Alain; Farinotti, Robert (Serv. Pharm., Hop. Pitie Salpetriere, Paris, 75013, Fr.). J. Chromatogr., 572(1-2), 195-202 (English) 1991. CODEN: JOCRAM. ISSN: 0021-9673.
AB The enantiomers of zopiclone were detd. in human plasma using a sequential achiral-chiral liq. chromatog. method. Zopiclone was sepd. from the biol. matrix and quantified on an achiral silica column. The limit of detection was 5 ng/mL. The eluent fraction contg. zopiclone was collected, evapd., reconstituted with the mobile phase and injected onto a chiral cellulose carbamate column where the enantiomeric ratio was calcd. This validated method, applied to a pilot study, suggests that pharmacokinetics of zopiclone is stereoselective.

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	34.67	36.92

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-9.29	-9.29

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L3 0 L1

Searched by: Mary Hale 308-4258 CM-1 12D16

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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.32      37.24

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)            SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                       0.00      -9.29

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DICTIONARY FILE UPDATES:  25 FEB 2002  HIGHEST RN 395638-68-3

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  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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CAS Registry Numbers that were added to the H/Z/CA/CAplus files between
12/27/01 and 1/23/02.  Use of the P indicator in online and SDI searches
during this period, either directly appended to a CAS Registry Number
or by qualifying an L-number with /P, may have yielded incomplete results.
As of 1/23/02, the situation has been resolved.  Also, note that searches
conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files
incorporating CAS Registry Numbers with the P indicator between 12/27/01
and 1/23/02, are encouraged to re-run these strategies.  Contact the
CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698,
worldwide, or send an e-mail to help@cas.org for further assistance or to
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L4            1 138680-08-7/RN

=> s l4 not l1
L5            1 L4 NOT L1

=> d ide can

L5   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   138680-08-7  REGISTRY
CN   1-Piperazinecarboxylic acid, 4-methyl-, (5R)-6-(5-chloro-2-pyridinyl)-6,7-
     dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1-Piperazinecarboxylic acid, 4-methyl-, 6-(5-chloro-2-pyridinyl)-6,7-
     dihydro-7-oxo-5H-pyrrolo[3,4-b]pyrazin-5-yl ester, (R)-
CN   5H-Pyrrolo[3,4-b]pyrazine, 1-piperazinecarboxylic acid deriv.
OTHER NAMES:


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CN (-)-Zopiclone
CN (R)-Zopiclone
FS STEREOSEARCH
MF C17 H17 Cl N6 O3
CI COM
SR CA
LC STN Files: ADISNEWS, BEILSTEIN*, BIOSIS, CA, CAPLUS, DRUGPAT, DRUGUPDATES, SYNTHLINE, TOXCENTER, TOXLIT, USPATFULL
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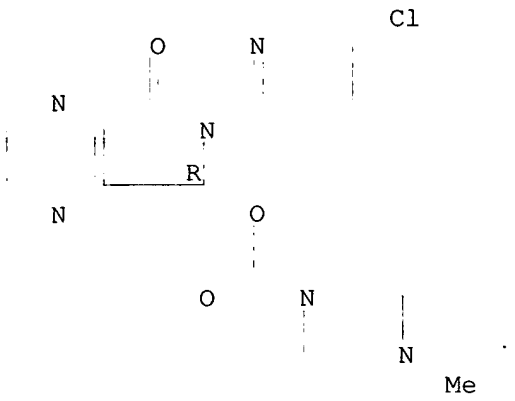
Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

24 REFERENCES IN FILE CA (1967 TO DATE)
24 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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REFERENCE 4: 133:183136

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REFERENCE 8: 130:261430

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REFERENCE 10: 129:140784

=> fil caplus;s l5;d 11-25 cbib abs

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	2.10	39.34

Searched by: Mary Hale 308-4258 CM-1 12D16

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-9.29

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FILE COVERS 1907 - 27 Feb 2002 VOL 136 ISS 9
FILE LAST UPDATED: 25 Feb 2002 (20020225/ED)

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The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the CAS files between 12/27/01 and 1/23/02. As of 1/23/02, the situation has been resolved. Searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator executed between 12/27/01 and 1/23/02 may be incomplete. See the NEWS message on this topic for more information.

L6 24 L5

L6 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2002 ACS
1997:808131 Document No. 128:106484 Separation of enantiomers of drugs by capillary electrophoresis V. Hydroxypropyl-.alpha.-cyclodextrin as chiral solvating agent. Koppenhoefer, Bernhard; Epperlein, Ulrich; Schlunk, Rainer; Zhu, Xiaofeng; Lin, Bingcheng (Auf der Morgenstelle 18, Institute for Organic Chemistry, University of Tubingen, D-72076 Tubingen, Germany). J. Chromatogr., A, 793(1), 153-164 (English) 1998. CODEN: JCRAEY. ISSN: 0021-9673. Publisher: Elsevier Science B.V..
AB In an extended chiral drug screening program, enantiosepn. of 86 racemic drugs was tested with hydroxypropyl-.alpha.-cyclodextrin as chiral solvating agent (CSA). A total of 34 drugs out of 86 could be resolved in this straightforward approach. The no. of expts. performed under identical conditions allows a correlation of the sepn. factors .alpha.m with the interaction strengths Rm. As shown for a subset of 23 drugs, the concn. of the CSA is a crucial parameter for further optimization.

L6 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2002 ACS
1996:668647 Document No. 125:339189 Capillary electrophoresis for separation of drug enantiomers using different cyclodextrins as chiral selectors.

Searched by: Mary Hale 308-4258 CM-1 12D16

Ji, Yibing; Chen, Yuying; Lin, Bingchen (Department Analytical Chemistry, China Pharmaceutical University, Nanjing, 210038, Peop. Rep. China). Zhongguo Yaoke Daxue Xuebao, 27(6), 363-365 (Chinese) 1996. CODEN: ZHYXE9. ISSN: 1000-5048.

AB Ten compds. were chirally sepd. by adding .alpha.-, .beta.-, .gamma.-cyclodextrin (CD) as chiral selector, resp. Due to the different cavity sizes, .alpha.-, .beta.-,, .gamma.-CD had different selectivities to the compds. with different sizes and shapes, and the "size-match" principle and complexation between CD and the guest compds. was introduced to explain the exptl. results. The chiral recognition mechanism was further proved.

L6 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2002 ACS

1996:580709 Document No. 125:264839 Development of a stereospecific radioimmunoassay for the analysis of zopiclone and metabolites in urine. Mannaert, Erik; Tytgat, Jan; Daenens, Paul (Lab. Toxicol., Kathol. Univ. Leuven, Louvain, B-3000, Belg.). Clin. Chim. Acta, 253(1,2), 103-115 (English) 1996. CODEN: CCATAR. ISSN: 0009-8981.

AB A sensitive and specific RIA has been developed, allowing the stereospecific detection of nanogram amts. of (+)- and (-)-enantiomers of zopiclone and its major metabolites in urine, without prior extn. or purifn. Antisera were obtained from two series of four rabbits, immunized with optically pure (+)- and (-)-N-hemisuccinyldesmethylzopiclone, conjugated to bovine serum albumin according to the active ester method. The assay was stereospecific, allowing discrimination between the two enantiomers of N-desmethylzopiclone with mutual cross-reactivities below 2%. Substantial cross-reaction was obsd. with the parent compd., although lower than expected, and to a lesser extent with the N-oxide metabolite. A selection of hypnotics, anxiolytics, antidepressants and some other widely used drugs did not interfere with the assay (<0 1%), when tested at a concn. level of 10 .mu./mL. The sensitivity of the assay was 50 pg/mL and 10 pg/mL for the (+)- and (-)-enantiomers, resp. The binding assay described here was used to evaluate the stereoselective excretion pattern of zopiclone. Anal. of cumulative excretion samples from a volunteer revealed a mean metabolic excretion ratio (+)/(-) of 2.2, ranging from 1.7 (7 h) to 4.4 (36 h). A mean excretion ratio of (+)/(-) of 2.5.+-.1 was calcd. for anal. of urine samples from 20 patients receiving zopiclone as a hypnotic daily.

L6 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2002 ACS

1996:460115 Document No. 125:184730 Semi-preparative chiral resolution of zopiclone and N-desmethylzopiclone. Mannaert, Erik; Daenens, Paul (Lab. Toxicol., Katholieke Univ. Leuven, Louvain, B-3000, Belg.). J. Pharm. Biomed. Anal., 14(8-10), 1367-1370 (English) 1996. CODEN: JPBADA. ISSN: 0731-7085.

AB Sepn. of the enantiomers was accomplished by liq. chromatog. using a com. available Chiralpak AS column. The asym. peak shape of (-)-N-desmethylzopiclone in comparison with that of (-)-zopiclone shows that the interaction of stereoisomers with the chiral stationary phase is crit. and often not predictable. Nonetheless, a max. load of 3 mg per injection could be achieved for the N-desmethyl metabolite. In one working week, about 100 mg of the enantiomers of N-desmethylzopiclone and about 50 mg of the enantiomers of zopiclone were collected in a pure state.

L6 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2002 ACS

1996:348014 Document No. 125:96309 Separation of enantiomers of drugs by capillary electrophoresis. III. .beta.-cyclodextrin as chiral solvating agent. Koppenhoefer, B.; Epperlein, U.; Christian, B.; Lin, B.; Ji, Y.; Chen, Y. (University of Tuebingen, Auf der Morgenstelle 18, Tubingen, D-72076, Germany). J. Chromatogr., A, 735(1 + 2), 333-343 (English) 1996. CODEN: JCRAEY. ISSN: 0021-9673.

Searched by: Mary Hale 308-4258 CM-1 12D16

AB Enantiomer sepn. by capillary zone electrophoresis was studied for a set of 34 chiral drugs. Keeping the concn. of .beta.-cyclodextrin as a chiral solvating agent as const. as possible led to the sepn. of 7 enantiomeric pairs. Carvedilol, tetryzoline, tropicamide and zopiclone gave a baseline sepn., chlorphenamine, ketamine, and orciprenaline a partial sepn. Statistical anal. revealed that the best sepn. factors were obsd. for a medium degree of interaction with the cyclodextrin. A theory explaining this effect provides a helpful guideline for further optimization.

L6 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2002 ACS

1996:77010 Document No. 124:193152 Enantioselective determination of zopiclone and its metabolites in urine by capillary electrophoresis. Hempel, G.; Blaschke, G. (Munster, D-48149, Germany). J. Chromatogr., B: Biomed. Appl., 675(1), 139-46 (English) 1996. CODEN: JCBBEP. ISSN: 0378-4347.

AB A method has been developed for the stereoselective detn. of zopiclone and its main metabolites in urine. After the addn. of the internal std. zolpidem the urine samples were extd. at pH 8 with chloroform-isopropanol (9:1). Analyses were carried out using capillary electrophoresis (CE) with .beta.-cyclodextrin as the chiral selector. The analytes were detected using UV laser-induced fluorescence detection with a He-Cd laser operated at 325 nm. Urine samples of two volunteers after oral administration of 7.5 mg zopiclone were investigated. The S-(+)-enantiomers of zopiclone and its metabolites were always excreted in higher amts. than the R-(-)-enantiomers. With the same method the zopiclone enantiomers were quantified in saliva. Compared to high-performance liq. chromatog., the CE method is very fast and simple.

L6 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2002 ACS

1995:713029 Document No. 123:132685 Degradation and racemization of zopiclone enantiomers in plasma and partially aqueous solutions. Fernandez, Christina; Gimenez, Francois; Mayrargue, Joelle; Thuillier, Alain; Farinotti, Robert (Service Pharmacie, Hopital Pitie-Salpetriere, Paris, Fr.). Chirality, 7(4), 267-71 (English) 1995. CODEN: CHRLEP. ISSN: 0899-0042.

AB We investigated the degrdn. and racemization zopiclone (ZOP) enantiomers in plasma and partially aq. solns. (ethanol:phosphate buffer). Degrdn. and racemization increased with increasing pH and temp. Degrdn. products were identified by means of mass spectrometry, which revealed hydrolysis of the carbamate function and opening of the pyrrolidone ring. In plasma, neither degrdn. nor racemization occurred after 6 mo of storage at -20.degree.C and subsequent extn.

L6 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2002 ACS

1995:713028 Document No. 123:123299 Solvent selectivity in chiral chromatography using a .beta.-cyclodextrin-bonded phase. Piperaki, Stavroula; Tsantili-Kakoulidou, Anna; Parissi-Poulou, Maria (Dep. Pharmacy, Univ. Athens, Athens, Greece). Chirality, 7(4), 257-66 (English) 1995. CODEN: CHRLEP. ISSN: 0899-0042.

AB A .beta.-cyclodextrin-bonded phase has been used to investigate the sepn. of the enantiomers of atenolol, oxprenolol, celiprolol, tertatolol, terbutaline, fluoxetine, norfluoxetine, and zopiclone, focusing on the importance of solvent selectivity. With cyclodextrin (CD)-bonded phases, chiral discrimination occurs because the two enantiomers of a racemate form inclusion complexes of different strengths within the CD cavity. The org. modifier mols. tend to compete with solutes for a definite no. of adsorption sites on the stationary phase. Moreover, the ternary complex formation may play an important role in chiral recognition. In this study, it was of interest to est. the influence of mobile phase modifiers with respect to solvent type (i.e., MeCN, MeOH, EtOH, THF, i-PrOH, PrOH and t-BuOH), size and shape, and concns. Solvent selectivity has been investigated by using different org. modifiers in mobile phases with the

same polarity, and relationships were established between the logarithm of solvent partition coeff. (log P2) and the three most important chromatog. parameters: retention time (t), resoln. (R), and enantioselectivity (.alpha.). Thus, it seems that they hydrophobicity of the org. modifier becomes one of the dominant factors affecting the inclusion process phenomena. Further, the apparent partition coeffs. of the compds. under study have been detd. and a comparison has been attempted regarding the degree of their enantiomeric resoln.

L6 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2002 ACS

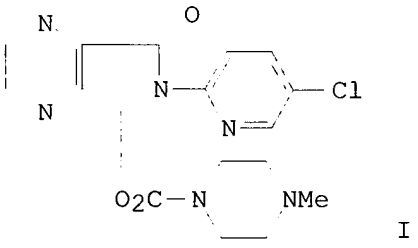
1994:594792 Document No. 121:194792 Stereospecific high-performance liquid chromatographic assay of zopiclone in human plasma. Foster, Robert T.; Caille, Gilles; Ngoc, Anh Ho; Lemko, Cathy H.; Kherani, Raheem; Pasutto, Franco M. (Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, T6G 2N8, Can.). J. Chromatogr., B: Biomed. Appl., 658(1), 161-6 (English) 1994. CODEN: JCBBEP.

AB A high-performance liq. chromatog. (HPLC) assay for the anal. of the enantiomers of zopiclone (ZPC), a cyclopyrrolone hypnotic, in plasma was developed. Following the addn. of chlordiazepoxide as internal std. (I.S.), plasma contg. the ZPC enantiomers and I.S. was extd. by liq.-liq. extn. at an alk. pH. After evapn. of the org. layer, the drug and I.S. were reconstituted in ethanol-hexane (80:20, vol./vol.) and injected onto the HPLC column. The enantiomers were sepd. at ambient temp. on a 25-cm Chiralcel OD-H column with ethanol-hexane (60:40, vol./vol.) as the mobile phase pumped at a flow-rate of 0.6 mL/min. The enantiomers of ZPC were quantified by fluorescence detection with excitation and emission wavelengths of 300 and 470 nm, resp. The assay described allows for the direct quantitation of ZPC without pre-column derivatization, and is suitable for clin. studies of ZPC in humans after administration of therapeutic doses.

L6 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2002 ACS

1994:235291 Document No. 120:235291 Pharmacokinetics of zopiclone and its enantiomers in Caucasian young healthy volunteers. Fernandez, C.; Maradeix, V.; Gemenez, F.; Thuillier, A.; Farinotti, R. (Serv. Pharm. Pharmacocinet., Hop. Pitie Salpetriere, Paris, 75651, Fr.). Drug Metab. Dispos., 21(6), 1125-8 (English) 1993. CODEN: DMDSAI. ISSN: 0090-9556.

GI



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AB The disposition of the enantiomers of zopiclone (I) and its two chiral metabolites was investigated after oral administration of a single dose of 15 mg of a racemic mixt. (twice the usual therapeutic regimen) in 12 adult Caucasian volunteers. Detn. of concns. of zopiclone enantiomers in plasma showed that zopiclone pharmacokinetics is stereoselective with AUC0-.infin. values of 691.3 and 209.5 ng.mL-1.h ($p < 0.001$), Cmax value of 87.3 and 44.0 ng.mL-1 ($p < 0.001$), oral CLtot/F values of 195.5 and 659.8 mL.min-1 ($p < 0.001$), Vd/F values of 98.6 and 192.8 L ($p < 0.01$) and

elimination half-life of 399.2 and 225.6 min ($p < 0.01$) for (+)-zopiclone and (-)-zopiclone, resp. On the contrary, absorption half-life and Tmax values were not significantly different. In 48-h urine, 3.6% of unchanged zopiclone was excreted, whereas 14.2% and 13.8% of both metabolites, N-desmethylzopiclone and N-oxideopiclone, resp., were found. Quantities of (+)-zopiclone excreted in urine were always higher compared with its antipode (-)-zopiclone for the 12 volunteers ($p < 0.001$). For the metabolites, quantities of both enantiomers were either equal or different and when different, it was always in favor of the (+)-enantiomer.

L6 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2002 ACS
1994:22978 Document No. 120:22978 Determination of the enantiomers of zopiclone and its two chiral metabolites in urine using an automated coupled achiral-chiral chromatographic system. Fernandez, Christine; Gimenez, Francois; Baune, Bruno; Maradeix, Valerie; Thuillier, Alain (Serv. Pharm., Hop. Pitie Salpetriere, Paris, 75013, Fr.). J. Chromatogr., Biomed. Appl., 617(2), 271-8 (English) 1993. CODEN: JCBADL. ISSN: 0378-4347.
AB The enantiomers of zopiclone and its two chiral N-desmethyl and N-oxide metabolites were detd. in urine using a coupled achiral-chiral liq. chromatog. method. After liq.-liq. extn., zopiclone and its two metabolites were quantified on a cyanopropyl column. After fluorimetric detection on the achiral system, the eluent was switched through a silica precolumn in order to trap and conc. the analytes. Each fraction was then backflushed sep. onto a carbamate cellulose chiral stationary phase in order to det. the enantiomeric ratios. The coupled system was automated with an autosampler and a switching value programmed by an integrator. The method was validated, and a first trial was performed on urine samples of a volunteer treated with 15 mg of racemic zopiclone.

L6 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2002 ACS
1993:463060 Document No. 119:63060 Treating sleep disorders, convulsive seizure, and other disorders using optically pure (-)-zopiclone. Young, James W.; Brandt, Steven (Sepracor, Inc., USA). PCT Int. Appl. WO 9310788 A1 19930610, 41 pp. DESIGNATED STATES: W: AU, BB, BG, BR, CA, CS, FI, HU, JP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, UA; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1992-US10705 19921201. PRIORITY: US 1991-801313 19911202.
AB (-)-Zopiclone (I) is a drug for treatment of sleep disorders and convulsive disorders. I is free of the side effects of (.+-.)-zopiclone. I is also useful for treating disorders affected by the agonist binding to central nervous system benzodiazepine receptors, such as anxiety and aggressive behavior.

L6 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2002 ACS
1992:591870 Document No. 117:191870 Preparation of (-)-zopiclone. Cotrel, Claude; Roussel, Gerard (Rhone-Poulenc Rorer S. A., Fr.). Eur. Pat. Appl. EP 495717 A1 19920722, 5 pp. DESIGNATED STATES: R: PT. (French). CODEN: EPXXDW. APPLICATION: EP 1992-400111 19920116. PRIORITY: FR 1991-490 19910117.
AB The title compd., prepd. by optical resoln. of racemic zopiclone as the D-(+)-O,O'-dibenzolyltartrate salt, is about twice as active as the racemate and had LD50 of .apprx.1.5 g/kg orally in mice.

L6 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2002 ACS
1992:75574 Document No. 116:75574 Determination of zopiclone enantiomers in plasma by liquid chromatography using a chiral cellulose carbamate column. Fernandez, Christine; Baune, Bruno; Gimenez, Francois; Thuillier, Alain; Farinotti, Robert (Serv. Pharm., Hop. Pitie Salpetriere, Paris, 75013, Fr.). J. Chromatogr., 572(1-2), 195-202 (English) 1991. CODEN: JOCRAM. ISSN: 0021-9673.

Searched by: Mary Hale 308-4258 CM-1 12D16

AB The enantiomers of zopiclone were detd. in human plasma using a sequential achiral-chiral liq. chromatog. method. Zopiclone was sepd. from the biol. matrix and quantified on an achiral silica column. The limit of detection was 5 ng/mL. The eluent fraction contg. zopiclone was collected, evapd., reconstituted with the mobile phase and injected onto a chiral cellulose carbamate column where the enantiomeric ratio was calcd. This validated method, applied to a pilot study, suggests that pharmacokinetics of zopiclone is stereoselective.

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